

From: [Maggie O'Grady](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Automatic reply: ICER Policy Summit Final Logistics
Date: Tuesday, December 04, 2018 11:57:35 AM

Thank you for your message. I will be out of the office until Monday, December 10th and may be delayed in responding to emails during this time.

If you need immediate assistance, please contact Laura Cianciolo at lcianciolo@icer-review.org.

From: [Maggie O'Grady](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Re: ICER Policy Summit Final Logistics
Date: Tuesday, December 04, 2018 12:02:13 PM

Hi Kaha,

The dress code is business casual.

Let me know if you have any other questions!

Best,
Maggie

Madeline O'Grady
Program and Event Coordinator
Institute for Clinical and Economic Review
2 Liberty Square
Boston, MA 02109
617-528-4013 x7029

From: Hizanishvili, Kaha (EHS) <kaha.hizanishvili@state.ma.us>
Sent: Tuesday, December 4, 2018 11:57 AM
To: Maggie O'Grady
Subject: RE: ICER Policy Summit Final Logistics

Hi Maggie,
Thank you for all the info!
A quick question – is there a “dress code” at the summit? i.e. should I pack business, business casual, or casual?
Thank you,
Kaha

From: Maggie O'Grady [mailto:mogrady@icer-review.org]
Sent: Tuesday, November 27, 2018 2:00 PM
To: Hizanishvili, Kaha (EHS)
Subject: ICER Policy Summit Final Logistics

Dear Kaha,

We are looking forward to seeing you next week at ICER's 2018 Membership Policy Summit on rebates! As the event is fast approaching, I am writing with some final logistics information.

- The summit will take place at the [Sheraton Grand at Wild Horse Pass](#), located at 5594 W. Wild Horse Pass Blvd, Phoenix, AZ 85226.

o You are confirmed to check in on **Wednesday, 12/5** and check out on **Friday, 12/7**.

Your confirmation number is: **1177315**

- The summit will begin on **Wednesday, 12/5** at **6:00 PM** with a welcome reception and dinner, and conclude after lunch at **1:00 PM** on **Friday, 12/7**.
- The hotel is located about a 20-minute drive from Phoenix Sky Harbor International Airport.

I am also reattaching a detailed agenda for the event and the background paper for your convenience. Please make sure to review these materials in advance of the meeting.

Please don't hesitate to reach out if you have any questions before the event. If you need assistance during the event, you can reach Celia Segel, ICER's Director of Policy Development, on her cell at 617-519-6273. I am looking forward to meeting you in person in December!

All the best,
Maggie

Madeline O'Grady

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mogrady@icer-review.org
www.icer-review.org

From: [Hizanishvili, Kaha \(EHS\)](#)
To: [Maggie O'Grady](#)
Subject: RE: ICER Policy Summit Final Logistics
Date: Tuesday, December 04, 2018 12:11:00 PM

Sounds good. Thank you!

From: Maggie O'Grady [mailto:mogradey@icer-review.org]
Sent: Tuesday, December 04, 2018 12:02 PM
To: Hizanishvili, Kaha (EHS)
Subject: Re: ICER Policy Summit Final Logistics

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www.icer-review.org

From: [Hizanishvili, Kaha \(EHS\)](#)
To: [Celia Segel](#)
Cc: [Steve Pearson](#); [Sarah Emond](#)
Subject: Re: Thank you!
Date: Tuesday, December 11, 2018 5:51:57 PM

Celia, Sarah and Steve,

Thank you so much for the invitation to your policy summit, the super interesting discussions and this very kind note!

I am impressed by level of participants and the degree of engagement ICER has generated within this forum. I found discussion very timely and informative. I am happy to be able to contribute to the discussion and very much looking forward to continue being engaged in the next steps.

Thank you!

Kaha

From: Celia Segel <csegel@icer-review.org>
Sent: Tuesday, December 11, 2018 2:41 PM
To: Hizanishvili, Kaha (EHS)
Cc: Steve Pearson; Sarah Emond
Subject: Thank you!

Kaha,

It was great to see you again last week, and thank you for making the trip out to Phoenix. You kept the room honest about how each of these approaches impacts Medicaid programs and their ability to capture the best price, and questioned key underlying assumptions to create better clarity in the room about the key options, helping us to reconsider how outcomes-based contracting fit into the overall picture. You reshaped our final discussion in a way that will absolutely be reflected in the final white paper.

We hope you enjoyed the conversation as much as we did. Thank you for everything you did in preparation for the meeting, and your participation throughout. Your perspective was invaluable to us, and we look forward to continuing to stay in touch as we revise this background paper, and put out the final version.

Celia, Sarah, and Steve

From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Cc: [Steve Pearson](#); [Sarah Emond](#)
Subject: Thank you!
Date: Tuesday, December 11, 2018 2:41:20 PM

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Celia, Sarah, and Steve

From: [Hizanishvili, Kaha \(EHS\)](#)
To: [Maggie O'Grady](#)
Subject: RE: ICER Policy Summit Final Logistics
Date: Wednesday, December 19, 2018 5:04:00 PM

Hi Maggie,
Hope all is well!
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Subject: Re: ICER Policy Summit Final Logistics

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From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Releases Draft Evidence Report on Treatments for Spinal Muscular Atrophy
Date: Thursday, December 20, 2018 5:48:25 PM



Institute for Clinical and Economic Review Releases Draft Evidence Report on Treatments for Spinal Muscular Atrophy

*-- Public comment period now open until January 31,
2019; Requests to make oral comment during public
meeting also being accepted --*

BOSTON, December 20, 2018 - The Institute for Clinical and Economic Review (ICER) today released a [Draft Evidence Report](#) assessing the clinical effectiveness and value of nusinersen (Spinraza®, Biogen) and onasemnogene abeparvovec (Zolgensma®, Novartis/AveXis) for the treatment of spinal muscular atrophy (SMA). Spinraza was approved in 2016 for treatment of SMA in both children and adults. Zolgensma is a gene therapy that has been studied in infants with Type I SMA, and an FDA decision is expected in the first quarter of 2019.

This draft report will be open to [public comment](#) until 5pm ET on January 31, 2019. Based on stakeholder feedback, ICER may revise key assumptions and findings for its Evidence Report, which will be published on February 21, 2019. The Evidence Report will be subject to deliberation during a public meeting of the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)), one of ICER's three independent evidence appraisal committees, on March 7, 2019.

ICER is committed to engaging with all stakeholders in a thorough and transparent manner. During this review, ICER has spoken with patients, clinical experts, insurers, and manufacturers. Public comments were also accepted on a Draft Scoping Document. The current draft report incorporates input received from patients, clinicians, and other stakeholders during each of these opportunities for engagement.

Submit a Public Comment

The [Draft Evidence Report](#) and [Draft Voting Questions](#) are now open to public comment until 5 PM ET on January 31, 2019. All stakeholders are invited to submit formal comments by email to publiccomments@icer-review.org. Guidelines for submitting public comments, including formatting specifications, are available on [ICER's website](#). ICER's [Manufacturer Engagement Guide](#) and [Patient Participation Guide](#) provide additional detail on what types of information may be most informative to the report.

ICER will review all comments and incorporate any necessary changes in the Evidence Report and Revised Voting Questions that will be posted on or about February 21, 2019. All comments and ICER's response to comments will be posted publicly along with the Evidence Report.

Register for the Public Meeting

The Evidence Report will be the subject of a public meeting of the New England CEPAC on March 7, 2019 in Boston, MA. During the meeting, the independent council will vote on key questions raised in the report. [Registration for the public meeting and live webcast is now open.](#)

Register to Make an Oral Comment

During the public meeting, there will be a limited amount of time available for interested stakeholders to make an oral comment on the report. Requests to submit oral comments must be emailed to publiccomments@icer-review.org by 5 PM ET on January 31, 2019. Individuals who wish to deliver oral comments must separately register to attend the meeting. For more information about registering for oral comment, [please visit our website.](#)

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website.](#)



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Institute for Clinical and Economic Review, Two Liberty Square,
Ninth Floor, Boston, MA 02109

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Sent by info@icer-review.org

From: [Lenz, Kimberly \(EHS\)](#)
To: [Sarah Emond](#)
Subject: quick question
Date: Thursday, December 20, 2018 8:34:00 AM

Hi Sarah,

Do you have a minute for a brief call?

Thanks!
Kim

Kimberly Lenz, PharmD
Clinical Pharmacy Manager, MassHealth

Office of Clinical Affairs
100 Hancock St, Quincy, MA 02171
Phone: 617-689-8777 | Fax: 617-847-3710
Email: Kimberly.Lenz@state.ma.us

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From: [Maggie O'Grady](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: RE: ICER Policy Summit Final Logistics
Date: Thursday, December 20, 2018 8:51:48 AM
Attachments: [ICER Travel Reimbursement Policy - External - July 2018.pdf](#)

Hi Kaha,

I'm attaching our reimbursement policy, which has a link to submit your receipts. Let me know if you have any questions about it!

Happy Holidays!

Maggie

Madeline O'Grady
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Institute for Clinical and Economic Review
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Institute for Clinical and Economic Review
Policy for Honoraria & Travel Expense Reimbursement
Updated July 2018

This policy applies for travel and honorarium (if applicable) for meeting participants at ICER Governance Board meetings, ICER Advisory Board Meetings, New England and Mid-West Comparative Effectiveness Public Advisory Council meetings, and California Technology Assessment Forum meetings. Public attendees of any ICER-sponsored meeting are not eligible for travel reimbursement. If you have any questions regarding your eligibility for travel reimbursement, please contact ICER.

- Travel expenses are reimbursed only for participants at ICER-sponsored meetings, including CEPAC, CTAF, MW CEPAC and Governance and Advisory Board Meetings.
- When pre-approval is required as noted below, it must be submitted to ICER 21 days in advance.
- Travel booked outside of the ICER process risks rejection of expense reimbursement request.
- Costs incurred due to changes to travel arrangements made less than 14 days prior to the meeting are the responsibility of the meeting attendee, and will not be reimbursed by ICER.
- A completed and signed W-9 form needs to be submitted in order to receive payment (required only if receiving an honorarium).

Domestic Air Travel

- Round-trip travel should be booked using discounted, non-refundable and non-transferable coach class tickets for scheduled meetings purchased at least 21 days prior to travel, as this will generally yield the lowest fare available. First class tickets will not be reimbursed. Upgrade purchases are not reimbursable.
- If the roundtrip ticket exceeds \$600, contact ICER to authorize issuing the ticket.
- ICER will reimburse for additional fees charged by the airlines for checked bags up to a one bag maximum. Overweight baggage fees will not be reimbursed.
- Avoid requesting paper tickets when making travel arrangements. ICER will not reimburse for paper ticket fees (issuance, overnight delivery, replacement if lost, etc.)
- Unreasonable airline change fees will not be reimbursed.
- Use of a private airplane will not be reimbursed. (*Just to be sure you're reading.*)

International Flights

- For purposes of this policy, flights to/from Canada are considered domestic. If other international travel is required, it must be pre-approved by ICER at least 30 days in advance.

Hotel/Lodging

- For many meetings, ICER will secure a hotel room block at a reduced rate and will notify participants well in advance. Stays at other hotels when ICER has secured a hotel room block will not be reimbursed without the prior approval of ICER.

- If no hotel block is reserved, lodging accommodations should be made at mid-price hotels; ICER will reimburse lodging expenses up to \$275 per day including all taxes in Boston, Massachusetts and comparable rates in other cities.
- ICER will reimburse traveler for usual and customary miscellaneous expenses related to travel in conjunction with ICER meetings. Allowable expenses in this category include:
 - Internet usage based on hotel's access charge and reasonable cost.
 - Customary gratuities for baggage handling, etc.

Meals

- ICER will reimburse for meals in conjunction with ICER-sponsored meetings at a rate of \$10 breakfast, \$15 lunch, \$25 dinner.
- ICER does not reimburse for meals taken in lieu of ICER-provided or sponsored meals, unless a dietary restriction necessitates it.
- ICER does not reimburse for alcoholic beverages.

Ground Transportation

- ICER will reimburse individuals traveling in conjunction with ICER-sponsored meetings via personal automobile at the published Internal Revenue Service rate per mile (currently \$0.545).
- Ground transportation to and from airports including ride sharing services, taxi or airport shuttle will be reimbursed.
- Livery service, limousines and private car service (executive sedan) will not be reimbursed, unless arranged by ICER.
- If a personal vehicle is used in lieu of airline travel, mileage reimbursement may not exceed the cost of the commercially discounted coach airfare 21 days prior to the trip.
- Parking and toll expenses will be reimbursed.
- Hotel shuttle vans and taxis/ride sharing services are the preferred mode of ground travel. Small groups who find that car rental is the most cost-effective option should contact ICER for approval prior to making the reservation. Rental cars are not eligible for mileage reimbursement at the IRS rate. Instead, ICER will reimburse the cost of the rental and fuel.
- Rail travel is permitted. Only coach and economy class fares will be reimbursed; business class and first-class upgrades are the responsibility of the traveler. However, Acela Business Class will be reimbursed if the trip is over 200 miles and the roundtrip cost does not exceed \$500.

Add-on Personal Travel

Add-on or personal travel is defined as travel either before or after ICER meetings that is scheduled at the sole discretion of the traveler. All expenses incurred with add-on travel are the responsibility of the traveler. You will be asked to provide a copy of a flight itinerary without the added personal travel to determine the reimbursable amount.

Expense Reporting & Receipts

- Expense reports will be provided by ICER following each meeting.
- Original or scanned original receipts are required for each travel expense item, including taxi fares.
- Expense reports are due to ICER within 30 days of the completed travel. This ensures timely reimbursement and accurate record keeping.
- Reimbursement checks are typically issued within 30 days of receipt of completed expense reports.

Contact: Questions or special requests can be directed to ICER's Finance Director at 617-528-4013 x 7024 or accounting@icer-review.org.

From: [Lenz, Kimberly \(EHS\)](#)
To: [Sarah Emond](#)
Subject: RE: quick question
Date: Thursday, December 20, 2018 9:27:00 AM

Let me see if I can summarize my question below to save you a call.

Does ICERs contextual value incorporate things like disability into the QALY calculation? Or would disability be incorporated in any other component of the value of a medication?

Thanks!
Kim

From: Sarah Emond [mailto:semond@icer-review.org]
Sent: Thursday, December 20, 2018 9:22 AM
To: Lenz, Kimberly (EHS)
Subject: RE: quick question

Sure – could do today after 1pm... 617-528-4013 x 7001.

From: Lenz, Kimberly (EHS) <kimberly.lenz@state.ma.us>
Sent: Thursday, December 20, 2018 8:34 AM
To: Sarah Emond <semond@icer-review.org>
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Subject: RE: quick question
Date: Thursday, December 20, 2018 9:22:26 AM

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To: [Lenz, Kimberly \(EHS\)](#)
Subject: RE: quick question
Date: Thursday, December 20, 2018 9:29:00 AM

Takes a call to explain! The answers is yes and yes. But it needs color commentary. Did you see our new QALY explainer? <https://icer-review.org/announcements/icer-describes-for-patients-and-policymakers-why-the-qaly-is-considered-the-best-way-to-reward-the-care-that-improves-patients-lives/>

From: Lenz, Kimberly (EHS) <kimberly.lenz@state.ma.us>
Sent: Thursday, December 20, 2018 9:27 AM
To: Sarah Emond <semond@icer-review.org>
Subject: RE: quick question

Let me see if I can summarize my question below to save you a call.

Does ICERs contextual value incorporate things like disability into the QALY calculation? Or would disability be incorporated in any other component of the value of a medication?

Thanks!
Kim

From: Sarah Emond [<mailto:semond@icer-review.org>]
Sent: Thursday, December 20, 2018 9:22 AM
To: Lenz, Kimberly (EHS)
Subject: RE: quick question

Sure – could do today after 1pm... 617-528-4013 x 7001.

From: Lenz, Kimberly (EHS) <kimberly.lenz@state.ma.us>
Sent: Thursday, December 20, 2018 8:34 AM
To: Sarah Emond <semond@icer-review.org>
Subject: quick question

Hi Sarah,

Do you have a minute for a brief call?

Thanks!
Kim

Kimberly Lenz, PharmD
Clinical Pharmacy Manager, MassHealth

Office of Clinical Affairs

100 Hancock St, Quincy, MA 02171
Phone: 617-689-8777 | Fax: 617-847-3710
Email: Kimberly.Lenz@state.ma.us

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From: [Maggie O'Grady](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Automatic reply: Your trip confirmation-LCXFWB 05DEC
Date: Thursday, December 27, 2018 4:31:21 PM

Thank you for your message. I will be out of the office until Wednesday, January 2nd, and will not be checking email during that time. I will respond to your message as soon as possible when I return.

From: [Hizanishvili, Kaha \(EHS\)](#)
To: accounting@icer-review.org
Cc: [Maggie O'Grady](#)
Subject: FW: Your trip confirmation-LCXFWB 05DEC
Date: Thursday, December 27, 2018 4:31:00 PM

Hi there,
Happy Holidays!

Please see attached receipt for my Boston-Phoenix roundtrip (\$376.40) – for December ICER Policy Summit.

My mailing address is:
Kaha Hizanishvili

Exemption C
[REDACTED]

Please let me know what additional information may be needed.

Thank you,
Kaha

Kaha Hizanishvili
Director of Strategy and Pharmacy Purchasing, MassHealth
Executive Office of Health and Human Services
One Ashburton Place, Boston, MA 02108
Tel: 617-573-1627
Email: Kaha.Hizanishvili@MassMail.State.MA.US

From: Kaha Hizanishvili [mailto:**Exemption C**]
Sent: Thursday, December 27, 2018 4:26 PM
To: Hizanishvili, Kaha (EHS)
Subject: Fwd: Your trip confirmation-LCXFWB 05DEC

----- Forwarded message -----

From: American Airlines <no-reply@notify.email.aa.com>
Date: Fri, Nov 9, 2018 at 1:51 PM
Subject: Your trip confirmation-LCXFWB 05DEC
To: **Exemption C**
[REDACTED]



Hello Kaha Hizanishvili!

Issued: Nov 9, 2018



Your trip confirmation and receipt

Record locator: **LCXFWB**

[Manage Your Trip](#)

Wednesday, December 5, 2018

BOS

9:20 AM

Boston

American Airlines 2229



PHX

1:28 PM

Phoenix

Seats: [24A](#)

Class: Economy (N)

Meals: Food For Purchase

[Free entertainment with the American app »](#)

Friday, December 7, 2018

PHX

4:30 PM

Phoenix

American Airlines 2763



BOS

11:13 PM

Boston

Seats: [20A](#)

Class: Economy (N)

Meals: Food For Purchase

Kaha Hizanishvili



Earn miles with this trip.

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Ticket # 0012320421135

Your trip receipt



Exemption C

Kaha Hizanishvili

FARE-USD	\$ 323.72
TAXES AND CARRIER-IMPOSED FEES	\$ 52.68
TICKET TOTAL	\$ 376.40

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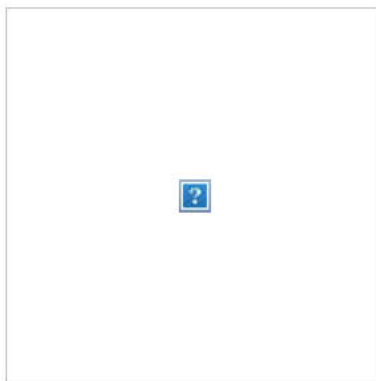
NRID: 5213644633420912474039600

From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Weekly View: January 4, 2019
Date: Friday, January 04, 2019 7:22:00 AM



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[**ICER Weekly View: January 4, 2019**](#)

From the desk of David Whitrap

Good morning and Happy New Year!

Each January brings optimism, fresh starts, and resolutions to be our best selves. It also sets up the annual battle: ***will our high-minded intentions be able to conquer well-entrenched habits?*** A new Congress was sworn in this week, but as of this moment, the government shutdown continues. Next week's JP Morgan Healthcare Conference may bring all sorts of bullish optimism for the biotech sector, but will those hopes be fueled by true scientific innovation or just speculation about the next megamerger? And ICER's own lofty mission -- to help all Americans achieve sustainable access to high-value care -- each year hurdles headfirst into a well-entrenched health system... a system that historically has struggled to discern when it's getting a great value for new medicines, and when it's getting ripped off by prices set far beyond the benefits patients actually receive. Check back next January and we'll let you know how we're doing.

Resolutions aside, let's take a quick look at what's happened since our last Weekly View:

- **ICER in the News:** Our draft assessment for spinal muscular atrophy, and our final report on biologic treatments for uncontrolled asthma.

- **Health Policy Updates:** The government shutdown's effect on federal health programs, the ongoing fight over the constitutionality of the ACA, and a rare lobbying loss for the drug industry.
- **Pharmaceutical Industry Trends:** Bristol's big bet on Celgene, the latest batch of January 1st price hikes, and the pros/cons of crowdfunding unproven medical treatments.

Now, on to the news.



Before the break, [ICER released our Draft Evidence Report](#) assessing the clinical effectiveness and value of nusinersen (Spinraza®, Biogen) and onasemnogene abeparvovec (Zolgensma®, Novartis/AveXis) for the treatment of **spinal muscular atrophy (SMA)**. The draft report, which is open for public comment through January, has been reported on by several media outlets, including [STAT News](#), [Reuters](#), [Bloomberg](#), [Investor's Business Daily](#),

[Endpoints News](#), [BioPharma Dive](#), [Vantage](#), and [BioSpace](#).

[Two high-priced drugs for spinal muscular atrophy are not cost effective, analysis concludes \(STAT\)](#)

Also before the break, [ICER released our Final Evidence Report and Policy Recommendations](#) on the biologic treatments for **uncontrolled asthma**, including dupilumab (Dupixent®, Sanofi/Regeneron), omalizumab (Xolair®, Genentech/Novartis), mepolizumab (Nucala®, GlaxoSmithKline), reslizumab (Cinqair®, Teva), and benralizumab (Fasenra™, AstraZeneca). While all five biologics modestly reduce asthma exacerbations and improve daily quality of life, each treatment would need a price discount of at least 50% to reach commonly cited thresholds for cost-effectiveness.



While the partial government shutdown does not affect the vast majority of the federal government's public health efforts, a few programs remain vulnerable (Kaiser Health News).

[How The Government Shutdown Affects Health Programs](#)

After a federal judge in Texas ruled that the entire Affordable Care Act was unconstitutional, a coalition of blue states is appealing the decision (Associated Press).

[Democratic attorneys general appeal Affordable Care Act ruling, as signups stay "remarkably steady"](#)

In a sprawling feature, STAT's Nick Florko chronicles PhRMA's unsuccessful fight against having to provide bigger discounts for Medicare Part D.

[How PhRMA finally lost: the inside story of the group's biggest lobbying failure in years](#)

Pharmaceutical Industry Trends

Yesterday morning, [Bristol-Myers Squibb announced its planned acquisition of Celgene for \\$74 billion](#). The team at STAT News analyzes what the megadeal means for the companies, the rest of the industry, and drug pricing: *"For anyone who thinks competition could help drive down cancer drug prices (tip: it has not), having two of the world's biggest cancer companies merge isn't going to improve things."*

[9 big takeaways from the \\$74 billion Bristol-Celgene deal](#)

Another new year, another wave of drug price increases. More than 250 drugs saw price increases during the first few days of January, although these increases were generally more modest than in previous years (The Wall Street Journal).

[Drugmakers Raise Prices on Hundreds of Medicines](#)

In a survey conducted by Cowen analysts, US payers are anticipating average annual drug price increases of 3-5%, and 5-7% on just the brand-name drugs (STAT News).

[Payers expect drug prices to rise 3 percent to 5 percent annually over the next three years](#)

Writing for NPR, Rachel Cohen explains why patients are crowdfunding unproven medical treatments, and why that's concerning.

[Crowdfunding Drives Funds And Attention Toward Questionable](#)

Medical Treatments

Regular readers of Weekly View will notice that the usual author of this newsletter, [Mitchell Stein](#), has stepped away from Weekly View to pursue other opportunities. We are forever grateful to Mitchell for helping ICER connect with each of you, and we remain committed to keeping everyone updated on ICER's activities and perspective.

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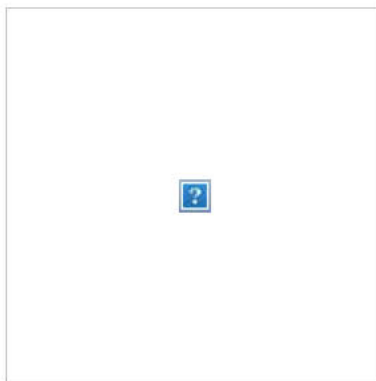
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From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Weekly View: January 11, 2019
Date: Friday, January 11, 2019 7:17:41 AM



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[ICER Weekly View: January 11, 2019](#)

From the desk of David Whitrap

Good morning, everyone. This week's JP Morgan Healthcare Conference brought us some big M&A deals, promising clinical trial data, and a slight ([okay, very slight](#)) improvement toward gender balance among the executives who presented.

Let's take a brief look at the news...



On the heels of Bristol-Myers Squibb's [announced bid](#) to purchase Celgene, Eli Lilly announced it's own plan to purchase Loxo Oncology, a company that has focused on developing cancer treatments that target a tumor's genetic markers regardless of where in the body the tumor is located (Wall Street Journal).

[Eli Lilly to Buy Loxo Oncology for \\$8 Billion in Cancer Bet](#)

Among all the #JPM2019 excitement, Sage Therapeutics announced positive Phase 3 data on its once-daily pill to treat women with postpartum depression (STAT).

[Sage Therapeutics Pill Improves Postpartum Depression in Pivotal Clinical Trial](#)

The Wall Street Journal described Bluebird Bio's desire to sell its potential gene therapy on a five-year installment plan. (Of course, even if the total cost is spread out over a period of time, ICER would still like the eventual price to align

with the therapy's ability to improve patients' lives.)

Biotech Proposes Paying for Pricey Drugs by Installment

And how could #JPM2019 be complete without Jamie Dimon himself weighing in on the state of the healthcare industry? The JP Morgan CEO spoke to pharma execs about his company's partnership with Amazon and Berkshire Hathaway to control health care costs (CNBC).

JP Morgan CEO Jamie Dimon Hosted a Private Dinner for Pharma Executives, and a Major Topic Was Amazon

Away from the conference, a new analysis suggests that annual price increases on existing drugs -- as opposed to the emergence of new treatments -- is the primary reason behind the significant year-over-year increase in prescription drug spending between 2008 and 2016. Keep in mind, however, that we're talking about the wholesale acquisition cost of these drugs, before rebates or discounts (NPR).

Prescription Drug Costs Driven by Manufacturer Price Hikes, Not Innovation

Fed up with the rising costs, new California Governor Gavin Newsom signed an executive order outlining several techniques that could help the state negotiate better drug prices (Reuters).

New California Governor Tackles Drug Prices in First Act

Louisiana is taking the next steps in its plan for a Netflix-inspired subscription model where the state would pay a single lump sum so that all people within the state's Medicaid program and prison system would gain access to hepatitis C treatment over the next five years (STAT).

Louisiana Proceeds with Plans for a 'Netflix' Subscription Model to Buy Hepatitis C Drugs

Over at Kaiser Health News, reporter Shefali Luthra describes her allergy to peanuts, as well as the hope and remaining unknowns offered by the forthcoming treatments (which ICER is [currently reviewing](#)).

Will I Always Face the Threat of a Peanut-Laden Kiss of Death?

And STAT News suggested that one of these companies focused on treating peanut allergy, Aimmune, may be experiencing some FDA delays due to the ongoing government shutdown.

Shutdown Has Aimmune Waiting on FDA on Multiple Fronts -- a Sign of Broader Delays for Pharma

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Images from Jon Testa, Chameleon Design, and SBRICONS from the Noun Project.

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Sent by info@icer-review.org

From: [Institute for Clinical and Economic Review](#)
To: [Lenz, Kimberly \(EHS\)](#)
Subject: ICER to Assess Whether the Most Significant Prescription Drug Price Increases Are Supported by New Clinical Evidence
Date: Thursday, January 17, 2019 2:50:14 PM



Institute for Clinical and Economic Review to Assess Whether the Most Significant Prescription Drug Price Increases Are Supported by New Clinical Evidence

*-- Public Comments on Draft Protocol Will Be Accepted
Through February 13, 2019 --*

BOSTON, January 17, 2019 - The Institute for Clinical and Economic Review ([ICER](#)) today posted a [draft protocol](#) describing a new annual analysis -- an ICER "Unsupported Price Increase" (UPI) report -- that will analyze significant prescription drug increases and determine whether or not new clinical evidence exists that could be used to support those increases. Public comment is being sought to inform a final version of the analytic protocol. Once finalized, the protocol will guide the development of the first of these annual reports, currently scheduled for October 2019.

"Drug prices are often increased substantially over time in the US, and questions are frequently raised regarding whether these price increases are justified," noted David Rind, MD, ICER's Chief Medical Officer. "By identifying drugs with substantial price increases despite no new evidence of added benefit, we hope to make an important first step in providing policymakers with information they can use to advance the public debate on drug price increases."

With guidance from a multi-stakeholder advisory group -- comprising representatives from patient advocacy groups, pharmaceutical companies, and payers representing both Medicaid and the private market -- ICER has developed a draft protocol for how it will conduct its UPI assessments. ICER proposes that its 2019 report will focus on up to 13 prescription drugs that experienced the most significant US price increases over the past 24 months, based primarily on which net price increases resulted in the largest overall budget impact for the US health system. ICER will review changes in the evidence base for each of these drugs and assess whether or not new clinical data exists that could suggest that the drugs could be significantly more beneficial for patients than what was previously understood.

A public comment period is now open for the [draft protocol](#), and ICER will consider all feedback when finalizing its methodology for this initiative. Comments can be

submitted by email to publiccomments@icer-review.org and must be received by 5 p.m. ET on February 13, 2019.

ICER anticipates publishing the final draft of its first UPI report in October. The complete timeline for this initiative is available [here](#).

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website](#).



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Cc: [Laura Cianciolo](#); [Steve Pearson](#); [Celia Segel](#); [David Whitrap](#); [Bill Dreitlein](#)
Subject: UPI Draft Protocol
Date: Thursday, January 17, 2019 10:10:30 AM
Attachments: [ICER UPI Draft Protocol 011719.pdf](#)
[ICER to Assess Whether the Most Significant Prescription Drug Price Increases Are Supported by New Clinical Evidence.msg](#)

Dear UPI Advisory Group –

Since we sent the last version of the UPI protocol to the ICER Methods Advisory Group and membership and received comments back, we have worked to revise the protocol.

As a next step, ICER will be posting a draft protocol for the UPI project later today as well as issuing a press release asking for comments from the public on the protocol. Both of these documents are attached but not yet public. As you will see in the timeline included in the draft protocol, the hope is to have the final protocol completed by early March, in time to start reviewing drugs in April.

Thank you so much for all your work on this so far. We may have additional questions for you after we get comments on the draft protocol, and we may also find as we proceed that we need to make modifications to the process even as it is underway (we specifically mention this possibility in the protocol). I hope if this occurs that we can involve you in thinking about changes.

We are excited to be close to actually starting the process of creating a UPI report. Please let me know if you have any thoughts, concerns, or questions.

-- David

David Rind, MD
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drind@icer-review.org
www.icer-review.org



Unsupported Price Increase Assessment

Draft Protocol

January 17, 2019

Institute for Clinical and Economic Review

Table of Contents

1. Background	1
2. List of Drugs to Review.....	3
3. Manufacturer Input	5
4. ICER Review.....	6
5. Designation of Drug Price Increases as “Unsupported”	7
6. Manufacturer Review Prior to Public Release	8
7. UPI Report Public Release	9
8. Changes in Process.....	10
References	11

1. Background

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue. For example, both California and Vermont now have laws tracking substantial drug price increases, requiring drug manufacturers to submit information that might justify increases above a certain threshold.¹⁻³ Despite these initiatives, there has been no systematic approach at a state or national level to determine whether certain price increases are justified by new clinical evidence or other factors. For several years, the Institute for Clinical and Economic Review (ICER) has received requests from state policymakers and others to fill this gap, but we had no dedicated funding or specified methodology to do so. Therefore, in 2017 we sought and received funding from the Laura and John Arnold Foundation to develop a new line of ICER reports evaluating selected high-impact drugs with substantial price increases. These new reports will seek to identify drugs for which there was no new clinical evidence that could support their price increases. These reports will be called Unsupported Price Increase (UPI) reports.

In mid-2018 we organized a multi-stakeholder advisory group to provide input into the design of a new approach for these reports. The advisory group was comprised of representatives from patient groups, drug makers, and insurers representing Medicaid and the private market. Working with this group over several months, ICER has developed a draft protocol for the UPI reports and is now seeking public comment before revising and finalizing its methods, with the first reports anticipated for mid-late 2019. Please see the figure below for an overview of the timeframe for the first UPI reports to be released later this year.

Milestone	Date
Draft Protocol	January 17
Public Comment Period	January 17 – February 13
Revised Protocol	March 8
Public Input Period on Drugs of Concern	March 15 – April 19
Manufacturer Notification and Input Phase I	May 6 – June 3
Preliminary Individual Assessments to Manufacturers	August 9
Manufacturer Input Phase II	August 9 – September 9
Final Report	October 8

As detailed below, ICER proposes to generate an annual report of up to 13 drugs that have experienced substantial price increases over a two-year time period. ICER will review changes in the evidence base for these drugs, and report on whether potential evidentiary support for price increases was found.

It is important to note that ICER does not have the capacity to perform full economic analyses on the large number of therapies that will be subject to analysis as part of this new report process, nor

would the time needed to develop full ICER reports provide information in a useful timeframe for the public and policymakers. Therefore, these UPI reports are not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER value-based price benchmark. Instead, we will focus the analysis on whether or not substantial new evidence exists that *could* justify its price increase. By identifying drugs with substantial price increases for which there is no basis in new evidence we hope to make an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

2. List of Drugs to Review

As described in greater detail below, the process for ICER’s review will start by identifying the top 100 drugs by sales revenue (administered in any setting) in the United States (US). From this list, the next step will be to identify drugs that have had list (wholesale acquisition cost or WAC) price increases over twice the medical Consumer Price Index (CPI) over a two-year period. Drugs with list price increases that meet this threshold will also have their two-year *net* price increase determined. We then rank drugs by the expected change in budget impact due to that change in net price over two years and select the top 10 drugs whose net price increase would have generated the largest increase in budget impact at the national level. We supplement that list with up to three additional drugs with substantial price increases based in part on public input.

2.1. Creating the List of Drugs with “Substantial” Price Increases

2.1.1. ICER will obtain a list of the 100 drugs with the largest dollar sales in the US. This information will come from SSR Health, LLC, the health care division of SSR, LLC, an independent investment research firm, and may leverage other data sources for companies that are not publicly traded. To derive a net price, SSR Health combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs.

2.1.2. ICER will determine WAC price changes for these drugs over the prior 24 months. The intent is to look at individual pricing decisions. As such, a rise in price across multiple manufacturers of a generic medication that in combination had a large change in budget impact would not be included in the review. For the first report we will be looking at price changes from January 1, 2017 through December 31, 2018.

2.1.3. ICER will determine which of these drugs have had a WAC price increase over the prior 24 months that exceeds two times the rate of medical care CPI (consumer price index). The medical care CPI is one of eight major components of the CPI recorded and reported by the United States Bureau of Labor Statistics (BLS).⁴ Medical care CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).⁵ Drugs whose WAC price increases have not exceeded two times the rate of medical care CPI will be removed from further evaluation. Our intent in choosing the overall medical care CPI and not its subcomponents is to reflect inflation in drug prices relative to inflation in the overall price of medical care.

2.1.4. Among those drugs with a WAC price increase greater than twice medical care CPI, ICER will determine *net* price changes over the prior 24 months. Net price information will be obtained from SSR Health. For drugs produced by companies that are not publicly traded, ICER will use prices from the Federal Supply Schedule (FSS).

2.1.5. ICER will rank those drugs whose net price increases have had the largest impact on US spending over the prior two years. To create this ranking, ICER will multiply the current annual

sales figure for each drug by its change in net price over 24 months. The top 10 drugs in this ranking will constitute the first part of the final list of drugs for which evidence review will be undertaken.

2.2. Additional Drugs to be Reviewed

We are aware that the public and policymakers may believe that there are drugs with significant price increases that do not meet the criteria for inclusion in this initial top 10 list. ICER may review up to three additional drugs. ICER will seek public input and consider adding drugs based on any of the following criteria:

- Drugs with extremely high price increases that do not have substantial budget impact at the national level
- Drugs used by millions of Americans with price increases that fell just below two times the medical care CPI
- Drugs whose price increases have important affordability implications for individual patients even if not for the health system
- Drugs whose price increases raise concerns about the fairness of the price increases.

2.3. Final List

The lists from 2.1 and 2.2 will be combined into a final list of up to 13 drugs for review. ICER will not publicly announce this list while the review is taking place as we heard concerns from manufacturers that being on the list would be stigmatizing when a determination has not yet been made as to whether the price increase is unsupported.

3. Manufacturer Input

ICER acknowledges that manufacturers may have information on their drugs and/or on competitor drugs that they believe justifies a substantial price increase. Manufacturers also have data on net price changes that may be more precise than data from SSR or FSS. ICER will seek to work with manufacturers to gain this information and the perspectives of manufacturers during the review process. Importantly, with the exception of clinical evidence submitted under [ICER's Academic-in-Confidence policy](#), any information provided by manufacturers will be included as part of the final report and will therefore be transparent to the public and policymakers.

Specifically, ICER will ask each manufacturer for the following information (which may be submitted under ICER's policy on academic-in-confidence data):

- New clinical evidence over the prior 36 months that demonstrates improved clinical or economic outcomes
- New evidence relating to comparator therapies that the manufacturer believes indicate new evidence of relative clinical advantages of their drug
- Other potential justifications for a price increase, including information within the prior 36 months related to:
 - a large increase in costs of production
 - large price savings attributable to the drug in other parts of the health system
 - all other reasons deemed relevant by the manufacturers.

Additionally, manufacturers will have four weeks from time of notification to provide input.

4. ICER Review

4.1. Overview of Review Process

For each drug ICER will determine the existing or new (within prior 36 months) indication(s) that comprise approximately 10% or more of the drug's use. To determine which indications meet this threshold, ICER will seek manufacturer input and elicit input from clinical experts and payers.

4.1.1. For these indications, ICER will seek to determine a “baseline” of known safety and clinical effectiveness as reflected in the evidence contained in the Food and Drug Administration (FDA) labeling information.

4.1.2. ICER will then perform independent systematic reviews looking for *new* information over the prior 36 months about benefits and harms of the reviewed drugs within these indications. The systematic review will look for information from randomized trials, high quality comparative observational studies, and, for information on low frequency harms, from large uncontrolled studies. ICER will assess the evidence from these systematic reviews and any supplemental evidence submitted by manufacturers to determine new information over the prior 36 months.

4.1.3. ICER will rate the quality of new evidence and the magnitude of added net health benefit. The quality of evidence will be rated using three-level GRADE as low, moderate, or high.⁶ GRADE is largely congruent with ICER evidence ratings and allows certainty in estimates of effect to be separated from the magnitude of benefit for this purpose.

For evidence that is rated as being of moderate or high quality, ICER will rate the additional net health benefit as none, small, or substantial using the usual ICER evidence matrix ratings.

ICER's usual evidence reports determine additional health benefit by comparing the new therapy to existing care options. However, for the UPI reports the comparison will be between previously understood net benefit for a therapy versus placebo and/or comparators and any new, additional net benefit for that same therapy based on newer evidence.

5. Designation of Drug Price Increases as “Unsupported”

Drugs found to have moderate/high quality new evidence of a substantial improvement in net benefit will be categorized as having a “price increase with new clinical evidence.” Drugs that have no new clinical evidence or clinical evidence that does not meet these criteria will be categorized as having unsupported price increases. As described earlier, all manufacturer information submitted to justify the price increase will be provided as a component of this report, but non-clinical rationales will not be evaluated by ICER as a determinant in whether the drug is categorized as having its price increase unsupported by clinical evidence.

6. Manufacturer Review Prior to Public Release

The manufacturer of each drug reviewed will be contacted individually and sent a preliminary version of the categorization and what the UPI report says about their drug. Each manufacturer will have four weeks to submit comments about their drug(s). These comments must be emailed as a PDF attachment to publiccomments@icer-review.org, must use Times New Roman 12-point font size, and must not be longer than five pages (excluding references and appendices). ICER will have previously asked manufacturers for information on indications of the drug that comprise 10% or more of the drug's use and will not accept information on new indications for review at this stage.

7. UPI Report Public Release

7.1 Public Release Process

7.1.1. With manufacturer input and further reflection, the report will be revised as necessary to produce a version for public release. The UPI Report will be the first public presentation of the results of the analysis that began with the identification of the top 100 drugs by sales in the US.

7.1.2. For the 10-13 drugs that comprise the final list, the UPI report will include current sales, the change in list price, and the change in net price. It will also include the funnel/flow from: largest dollar sales; to largest changes in WAC; to largest changes in net price for those drugs with WAC changes exceeding two times medical CPI; to largest impact on spending. This will show how the list was culled from the original 100 drugs to the 10-13 reviewed drugs.

The report will present the reviews/categorizations of up to 13 drugs. As noted, earlier, manufacturer comments will be published along with ICER's responses to those comments as an Appendix.

8. Changes in Process

Despite benefiting from the input of our advisory group, we expect that we will encounter situations throughout the first year of the UPI review that have not been fully anticipated. Thus, it should be expected that the UPI process will change after the first year of implementation. Even during the first year of the UPI report process, ICER will be monitoring aspects of the process as it progresses and may need to alter aspects of the review if needed to maintain transparency and fairness to all parties. ICER commits to flexibility within this first review and to transparency about any needed changes.

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From: ICER <info@icer-review.org>
Sent: Wednesday, January 16, 2019 3:19 PM
To: David Whitrap
Subject: ICER to Assess Whether the Most Significant Prescription Drug Price Increases Are Supported by New Clinical Evidence



Institute for Clinical and Economic Review to Assess Whether the Most Significant Prescription Drug Price Increases Are Supported by New Clinical Evidence

*-- Public Comments on Draft Protocol Will Be Accepted
Through February 13, 2019 --*

BOSTON, January 17, 2019 - The Institute for Clinical and Economic Review ([ICER](#)) today posted a [draft protocol](#) describing a new annual analysis -- an ICER "Unsupported Price Increase" (UPI) report -- that will analyze significant prescription drug increases and determine whether or not new clinical evidence exists that could be used to support those increases. Public comment is being sought to inform a final version of the analytic protocol. Once finalized, the protocol will guide the development of the first of these annual reports, currently scheduled for October 2019.

"Drug prices are often increased substantially over time in the US, and questions are frequently raised regarding whether these price increases are justified," noted David Rind, MD, ICER's Chief Medical Officer. "By identifying drugs with substantial price increases despite no new evidence of added benefit, we hope to make an important first step in providing policymakers with information they can use to advance the public debate on drug price increases."

With guidance from a multi-stakeholder advisory group -- comprising representatives from patient advocacy groups, pharmaceutical companies, and payers representing both Medicaid and the private market -- ICER has developed a draft protocol for how it will conduct its UPI assessments. ICER proposes that its 2019 report will focus on up to 13 prescription drugs that experienced the most significant US price increases over the past 24 months, based primarily on which net price increases resulted in the largest overall budget impact for the US health system. ICER will review changes in the evidence base for each of these drugs and assess whether or not new clinical data exists that could suggest that the

drugs could be significantly more beneficial for patients than what was previously understood.

A public comment period is now open for the [draft protocol](#), and ICER will consider all feedback when finalizing its methodology for this initiative. Comments can be submitted by email to publiccomments@icer-review.org and must be received by 5 p.m. ET on February 13, 2019.

ICER anticipates publishing the final draft of its first UPI report in October. The complete timeline for this initiative is available [here](#).

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website](#).



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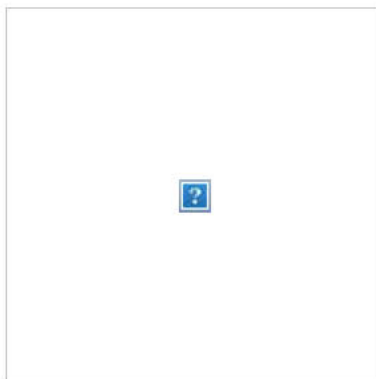
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To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Weekly View: January 18, 2019
Date: Friday, January 18, 2019 7:17:55 AM



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[ICER Weekly View: January 18, 2019](#)

From the desk of David Whitrap

Good morning everyone. Here in Boston, we've seen exactly 0.2 inches of snowfall this winter. For those keeping score at home, that's 22.7 inches less than what we'd seen by this time last year, and it's half of what's already fallen this season in famously frigid cities like El Paso and Tucson. It's like the weather around here just decided to shut down, right alongside the federal government.

Well, things might be changing this weekend, as local meteorologists are predicting that clouds are ready to open and dump up to two feet of snow on parts of Massachusetts. Could this be a sign that the government is finally ready to open back up, too? Probably not. But on behalf of those 800,000 affected federal employees, I sure hope so.

This week we'll look at:

- **ICER in the News:** Our new initiative to study "Unsupported Price Increases," the draft scope for our planned assessment of treatments for Duchenne muscular dystrophy, California dreamin' about finding some negotiating leverage, and NBC Nightly News' look at the clinical and economic value of the first gene therapy.
- **Pharmaceutical News:** Lessons Medicare can learn from the V.A., a split-decision at an FDA Advisory Committee meeting, the shutdown's potential

slowdown of other FDA reviews, and how the US health system can achieve more cost savings from approved biosimilars.



Yesterday afternoon, ICER announced that we will begin to [assess whether the most significant drug price increases are supported by emerging evidence](#) that could be used as clinical justification for the higher price. We are accepting public comment on our draft protocol through February 13th. Look for our first annual "**Unsupported Price Increase**" report by the end of October.

ICER also posted a [Draft Scoping Document for our assessment of treatments for Duchenne muscular dystrophy](#). Our review will focus on eteplirsen (Exondys 51™, Sarepta Therapeutics), golodirsen (Sarepta Therapeutics), and deflazacort (Emflaza®, PTC Therapeutics). Public comment on the scope of this assessment must be received by February 1.

Last week, new California Governor Gavin Newsom signed an executive order

aimed at lowering drug costs by having the state's various public -- and potentially private -- payers band together to increase negotiating leverage with pharmaceutical companies. The New York Times spoke with several industry experts, including ICER's Steve Pearson, about the potential implications.

California Adds Its Clout to States Battling High Drug Prices (The New York Times)

On Wednesday evening, NBC Nightly News aired a segment about Luxturna, the gene therapy that treats an inherited form of blindness. Incorporating ICER's value assessment and a brief interview with Steve Pearson, the segment reflects the tension between the treatment's innovative science, its potential benefits for patients, and its unprecedentedly high price.

This Gene Therapy Treatment for Blindness Is the Most Expensive Drug in America (NBC Nightly News)

A new analysis suggests that Medicare Part D would have saved \$14.4 billion on its top 50 pills in 2016 -- a 44% discount -- if the program had obtained the same prices as the Department of Veterans Affairs. *(In 2017, [the V.A. began using ICER's assessments](#) to help inform its coverage policies and price negotiations.)*

Medicare Part D could have saved \$14.4 billion in 2016 by negotiating as the VA did (STAT)

The FDA Advisory Committee provided an 8-8 split-decision on whether to recommend approval of what would be the first oral medication for Type 1 diabetes. The agency is likely to decide by the end of March if the drug will reach the US market.

F.D.A. Panel Splits on Whether to Approve New Diabetes Drug (The New York Times)

Last week, we mentioned how the government shutdown may slow the FDA's review of Aimmune's treatment for peanut allergy. This week brings news that several other treatments may also be affected.

[If the shutdown drags on at FDA, it will put anticipated new treatments in jeopardy \(STAT\)](#)

And while negotiations around the shutdown seem to be stalled indefinitely, the two political parties are continuing to discuss various approaches to manage drug prices.

[Dem chairman Cummings meets with Trump health chief to discuss drug prices \(The Hill\)](#)

At an industry conference earlier this week, HHS Secretary Alex Azar acknowledged the need for pharmacy-level interchangeability of biosimilars, so "PBMs can break through the rebate wall, confident they can move share to the biosimilar."

[Medicare IPI Model Could Import Benefit Of Biosimilar Competition, Azar Suggests \(Pink Sheet\)](#)

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From: [Institute for Clinical and Economic Review](#)
To: [Lenz, Kimberly \(EHS\)](#)
Subject: ICER Launches International Collaborative to Develop New Methods to Guide Value-Based Pricing of Potential Cures
Date: Wednesday, January 23, 2019 10:08:40 AM



Institute for Clinical and Economic Review Launches International Collaborative to Develop New Methods to Guide Value-Based Pricing of Potential Cures

*-- NICE in the UK and CADTH in Canada among
international agencies participating; Public input on key
methodological issues is being accepted through February
20, 2019 --*

BOSTON, January 23, 2019 - The Institute for Clinical and Economic Review ([ICER](#)) today announced [a new project](#) to develop and test alternative methods for the evaluation of potentially curative treatments and for translating the results of cost-effectiveness analyses into recommendations for value-based price benchmarks. In this work, ICER will collaborate with methodology experts, stakeholders, and several leading international health technology assessment (HTA) groups, including both the United Kingdom's National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH). The goal of this initiative is to ensure that assessment methods are tailored appropriately to the distinctive nature of the evidence base for potential cures. The initiative will inform ICER's 2019 update to its value assessment framework while seeking to build consensus across HTA groups in anticipation of a rising tide of gene therapies and other potential cures.

"Patients and those who care for them eagerly anticipate the coming wave of treatments that may cure a wide range of illnesses," said Steven D. Pearson, MD, MSc, President of ICER. "The science is undeniably exciting. But when these treatments are first launched, which is when pricing and coverage decisions have to be made, the evidence on the long-term value of these treatments may be extremely limited. Given the stakes for patients, and the high prices that one-time curative treatments are likely to command, we are taking the lead now to assemble and work with key experts to ensure we are using the best possible methods for assessing the value of these treatments. If we don't, we risk undervaluing potential cures, or over-valuing them, either of which would ultimately harm patients and the health care system as a whole. Exploring different approaches to assess the value of potential cures, and building some early consensus across groups that will be doing this work in the US and internationally, will be essential to arm the policymaker, payer, and manufacturer communities with a platform that can reward

innovation while supporting a sustainable health insurance system."

An open input period is now open during which ICER hopes to receive ideas and guidance regarding the key methodological questions highlighted below:

- *How should value-based prices for potential cures reflect substantial uncertainty regarding clinical safety and effectiveness due to limitations in study design, outcome measures, and the size and duration of clinical trials?*
- *How should value-based prices for potential cures reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?*
- *How should value-based prices for potential cures reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies?*

Comments can be submitted by email to publiccomments@icer-review.org and to be integrated usefully into the research effort must be received by 5 p.m. ET on February 20, 2019. ICER will post a draft white paper for additional public comment sometime this summer, before finalizing the white paper and methodology recommendations before the end of the year.

This initiative is made possible with financial support from the [Commonwealth Fund](#) and the [National Institute for Health Care Management](#).

About ICER

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To: [David Rind](#); [Andreas Kuznik](#); [Anna Kaltenboeck](#); [Dan Danielson](#); [David Mitchell](#); [Jane Horvath](#); [Hizanishvili, Kaha \(EHS\)](#); [Leah McCormick Howard](#); [Susan Shiff](#)
Cc: [Laura Cianciolo](#); [Steve Pearson](#); [Celia Segel](#); [David Whitrap](#); [Bill Dreitlein](#)
Subject: RE: UPI Draft Protocol
Date: Wednesday, January 23, 2019 12:51:00 PM

David,
Nice work. Thanks.
Paul

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Sent: Thursday, January 17, 2019 10:10 AM
To: Andreas Kuznik; Anna Kaltenboeck; Dan Danielson; David Mitchell; Jane Horvath; Hizanishvili, Kaha (EHS); Leah McCormick Howard; Jeffrey, Paul (EHS); Susan Shiff
Cc: Laura Cianciolo; Steve Pearson; Celia Segel; David Whitrap; Bill Dreitlein
Subject: UPI Draft Protocol

Dear UPI Advisory Group –

Since we sent the last version of the UPI protocol to the ICER Methods Advisory Group and membership and received comments back, we have worked to revise the protocol.

As a next step, ICER will be posting a draft protocol for the UPI project later today as well as issuing a press release asking for comments from the public on the protocol. Both of these documents are attached but not yet public. As you will see in the timeline included in the draft protocol, the hope is to have the final protocol completed by early March, in time to start reviewing drugs in April.

Thank you so much for all your work on this so far. We may have additional questions for you after we get comments on the draft protocol, and we may also find as we proceed that we need to make modifications to the process even as it is underway (we specifically mention this possibility in the protocol). I hope if this occurs that we can involve you in thinking about changes.

We are excited to be close to actually starting the process of creating a UPI report. Please let me know if you have any thoughts, concerns, or questions.

-- David

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From: [David Rind](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: RE: UPI Draft Protocol
Date: Thursday, January 24, 2019 10:31:59 AM

Thanks!

-- David

From: Jeffrey, Paul (EHS) <paul.jeffrey@state.ma.us>
Sent: Wednesday, January 23, 2019 12:51 PM
To: David Rind <drind@icer-review.org>; Andreas Kuznik <andreas.kuznik@regeneron.com>; Anna Kaltenboeck <kaltenba@mshcc.org>; Dan Danielson <Dan.Danielson@PREMERA.com>; David Mitchell <david@patientsforaffordabledrugs.org>; Jane Horvath <JHorvath@nashp.org>; Hizanishvili, Kaha (EHS) <kaha.hizanishvili@state.ma.us>; Leah McCormick Howard <lhoward@psoriasis.org>; Susan Shiff <susan.shiff@merck.com>
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From: [Celia Segel](#)
To: [Steve Pearson](#)
Subject: Feedback on Final Draft of Rebates Paper
Date: Friday, January 25, 2019 3:03:42 PM
Attachments: [Final Draft - ICER OHE White Paper on Rebates.pdf](#)
[ATT00001.htm](#)

Dear Members,

I am pleased to present our final draft of the post-Summit white paper on alternatives to rebates. We learned a huge amount from all of your expertise during the summit, so before we circulate this paper more broadly to the public, we hope you will provide us with one more round of commentary. Please note that this final draft should be kept internal to your organizations as it is not yet public.

Please send us your comments and edits on this final draft no later than February 8.

We have greatly enjoyed hearing your insights onto this very important and timely topic. We look forward to hearing your thoughts on this final paper.

Celia Segel

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VALUE, ACCESS, AND INCENTIVES FOR INNOVATION: POLICY PERSPECTIVES ON ALTERNATIVE MODELS FOR PHARMACEUTICAL REBATES

January 2019

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TABLE OF CONTENTS

Executive Summary.....	ES1
1. Introduction.....	1
1.1. Context.....	1
1.2. Our Approach.....	2
1.3. How do rebates work?	3
1.4. History of the Transition from Discounts to Rebates	4
1.5. Perspectives on the “Gross-to-Net” Price Gap	5
2. Rebates in Different Insurance Markets.....	7
2.1. Medicaid	9
2.2. Medicare	10
2.3. Commercial Markets.....	11
Flow of rebates from PBMs to payers	11
Flow of rebates from PBMs and payers to patients	12
3. How do rebates impact different stakeholders?	13
3.1. Empirical studies on the impact of rebates	13
3.2. Rebates and the Flow of Revenue Within the Pharmacy Supply and Financing System.....	14
3.3. Public Comments on Rebate System Alternatives from Different Stakeholders.....	15
4. Key aspects for consideration of reform	16
4.1. Transparency of Rebate Amounts	16
4.2. Maintaining the possibility of implementing outcome-based contracts.....	17
5. What are the alternative options for rebate models?	18
5.1. Major Considerations for Alternative Rebate Models.....	19
5.2. OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)	19
5.3. OPTION 2: Point of Sale (POS) rebates for patients.....	21
5.4. OPTION 3: Eliminate rebates and move to upfront discounts	24
5.5. A Summary of the Three Alternative Options against Relevant Criteria.	26
6. Discussion	28
7. References	32

Executive Summary

The combination of rising drug costs at the health system level and increasing financial stress for individual patients has triggered intense national concern. One target has come under particular scrutiny: rebates.

Drug makers and payers (including both insurers and pharmacy benefit managers [PBMs]) negotiate discounts to the list price of drugs (rendered post-sale as rebates) in exchange for preferential formulary placement which increases sales. Rebates are a key negotiating tool for payers, and help produce a lower “net” price for drugs that can help reduce the overall costs of drug spending. But for many years the PBM business model has included a revenue stream gained by retaining a small percent of the absolute rebate amount they return to plan sponsors. Drug makers argue that this “rebate economy” forces them to increase list prices in order to offer ever larger rebates to PBMs to gain preferred formulary status. The effect of rebates in lowering net prices may reduce plan sponsor costs and therefore help moderate the cost of insurance premiums for all plan members, but higher list prices hurt those patients who need ongoing drug treatment, since patients are required to pay their out-of-pocket share for drug coverage in relation to the list price, not the negotiated rebate price.

Rebates have therefore become an extremely contentious topic, praised by many as the best tool available to provide competitive leverage for payers seeking lower net prices, but reviled by others who view it as the chief sin in a system that punishes sick patients with higher out-of-pocket costs and absorbs billions of dollars that could otherwise either reward innovation or keep costs down, or both. Recently, both payers and drug makers have introduced new approaches that experiment with alternative approaches to rebates. Meanwhile, the Trump administration is exploring regulatory action that could lead to dramatic changes to rebates. But what is known about how the rebate system interacts with other elements of drug pricing, coverage and delivery? And, for different stakeholders, what are the potential benefits and possible negative consequences of realistic possible alternatives? This White Paper, benefitting from interviews with numerous participants in the rebate process – from plan sponsors, to insurers, to PBMs, to drug makers – addresses these questions and lays out a framework for evaluating proposed alternatives to a rebate model that has served as the cornerstone of drug pricing and coverage negotiation for decades.

What are the major alternative options for rebate models?

There are three major alternative options to the current rebate model. The first two options represent rebate “reform” and may be combined, but it is important for policy makers to consider the potential advantages and disadvantages of each element separately. The third option would involve eliminating rebates.

OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)

The first option is to require that PBMs pass 100% of rebates through to plan sponsors in order to eliminate the incentive for PBMs to develop formularies that drive utilization to highly rebated drugs despite higher net costs for payers. PBMs would be paid instead solely through fees from plan sponsors. Although arrangements between PBMs and health plans which specify 100% pass-through of rebates are already becoming more common, a more universal requirement could be linked to a move to flat fees for distributors and pharmacies, helping to wean the entire drug delivery chain off of reliance on rebates and percentage fees.

Potential advantages: With less incentive for PBMs to develop rebate-driven formularies, financial incentives for high list prices will diminish, benefiting individual patients financially if their cost-sharing is linked to list price (which could lead to better adherence and outcomes). Net prices could remain confidential, and rebates could, in principle, continue to be linked to formulary placement and utilization at the population level. Proponents also believe that passing all rebates – and any other form of manufacturer fee or payment – back to plan sponsors would allow payers to compare PBM offerings more transparently and improve the negotiating power of payers over the rewards of PBMs and others in the delivery chain. This alternative rebate model could also improve transparency for the individual payer so that they understand why certain decisions are being made by a PBM with regards to formulary design.

Another potentially beneficial effect of moving to a universal pass-through model is that PBMs might then need to compete more directly on patient management and the value for money of the drugs utilized. Without rebates, PBMs might put more emphasis on distinguishing themselves in the marketplace by achieving superior patient outcomes, for example through methods such as provider education and helping ensure patients receive and take their medications. It could also facilitate adoption of value-based formularies based on cost-effectiveness, although use of post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign.

The implementation of this model would involve relatively little disruption to the overall drug delivery system but would still entail a difficult transition from existing contracts without a 100% pass-through.

Potential disadvantages: This alternative model would achieve little for patients in the short term if the increased rebates flowing back to plan sponsors are not reflected in lower co-pays (i.e. if this reform were not implemented alongside requirements around applying rebates to the point of sale – see option 2). The potential impact on the gross-to-net gap and overall spending is also unclear because many plans now expect, and some may prefer, to have large and guaranteed rebates.

In addition, the primary potential advantage of a pass-through model may also represent one of its greatest potential disadvantages for both payers and patients. If PBMs are paid a fixed fee independent of negotiated rebates, they could have less incentive to put great effort into fighting for the lowest net price.

Further, it is important to consider whether requiring PBMs to pass along all rebates to plan sponsors might limit PBMs efforts to benefit from economies of scale to achieve greater savings beyond what a single plan could on its own. If PBMs are prohibited from aggregating rebates across multiple Part D plans, it might lead to a reduction in negotiating leverage, and therefore higher overall net costs for payers and plan members.

Finally, these reforms will not impact Medicare plans as the law already requires that payers who participate in Medicare Part D pass all negotiated discounts (direct and indirect remuneration [DIR]) back to the government.

OPTION 2: Point of Sale (POS) rebates for patients

POS rebates involves passing rebate savings directly to patients. This option appears to most directly address the problem of high out-of-pocket costs, and some plans already offer, or are experimenting with, POS rebates. However, systems are not generally set up to provide a POS rebate for individual patients, since many rebates are tied to utilization at the group/population level and are determined post hoc. Therefore, it is difficult to assign a precise rebate level for a drug at the POS.

Potential advantages: Action taken to require POS rebates with any rebate at the payer level could have several important advantages. First, patients who require extended use of expensive medications for chronic conditions could have their financial burden lessened. Whilst the evidence is limited, there is some indication that POS rebates could improve adherence and consequently clinical outcomes. Second, aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies if patient co-pays are lowest, as a consequence of the POS rebates, for the most cost-effective treatment.

Potential disadvantages: Some commentators worry that POS rebates would include information for patients that inadvertently discloses the gross to net price gap, thereby eliminating confidentiality of the rebate level and undermining the negotiating power held by payers through their ability to get confidential rebates. In addition, POS rebates by themselves are not a cure for the financial burdens faced by many patients who need high-cost medicines but only have access to health insurance benefit designs with high deductibles and/or co-insurance. POS rebates would also not neutralize the incentives for PBMs and others in the drug delivery chain that may lead them to seek higher list prices and larger rebates.

POS rebates give to individual patients some of the money that would otherwise flow back to the plan sponsor. The payer no longer has the option to apply those funds in ways that reduce overall health insurance premiums, which some stakeholders view as the priority for any change to the current rebate system. Another potential risk is that unless POS rebates are carefully calibrated, they could reduce the out-of-pocket cost of a branded drug to the extent that these are chosen by members in place of generics that cost less to the plan.

Applying rebates at the point of sale will reduce out-of-pocket cost for specific individuals who are on high cost medications but would not impact the most economically vulnerable patients on Medicaid, whose copayments are kept low already. For these patients, as well as others who have reached their out-of-pocket maximums in their respective plans, the rebate savings will continue to flow directly to the payer.

Multiple potential disadvantages have been noted if POS rebates were implemented for patients in Medicare Part D. Some fear that POS rebates would lead plans to increase premiums enough to have an important negative impact on the affordability of Medicare Part D plans for financially vulnerable patients.

OPTION 3: Eliminate rebates and move to upfront discounts

Although most stakeholders believe that eliminating rebates in favor of upfront discounts would prove the most disruptive possible alternative model to the current rebate system, some commentators believe that moving to upfront discounts is both feasible and the best way to accomplish the chief aims of many stakeholders.

Potential advantages: The main argument for upfront discounts in place of rebates is that it removes the PBM incentive to generate revenue from the gross to net gap that many feel can lead to higher list prices and a less transparent flow of money between manufacturers, PBMs, and payers. Upfront discounts could also be the alternative model that most facilitates the application of cost-effectiveness findings to the development of formularies. Since the effective price is known at the outset, cost-effectiveness can be determined and compared. Discounts could be allowed to vary depending on clear criteria such as cost-effectiveness or expected volume. Clinicians could more readily become involved in choosing the most cost-effective treatment for their patients.

Potential disadvantages: Many have argued that upfront discounts would not provide the same level of negotiating power as rebates that can be linked to utilization/market share. The implicit transparency in upfront discounts is also viewed as problematic, potentially leading manufacturers to set single discount levels for all payers that would also increase costs. Some have argued that publishing discounts would increase the risk of tacit collusion on price discounting among competing manufacturers.

In the legal settlement 22 years ago that led to the abandonment of discounts in favor of rebates, drug manufacturers agreed they would not offer upfront volume discounts, and instead agreed to offer similar pricing contracts to all purchasers that demonstrated they could move market share. The legal context has not changed, so it is not clear whether manufacturers could legally offer upfront any differentiation of discounts without violating antitrust law.

In addition, from a practical perspective, a move to a fixed-price discount approach is viewed by all stakeholders as requiring a major, complicated restructuring of both Medicare Part D and commercial contracts. Wholesalers and pharmacies could end up dealing with dozens of different (discounted) prices for each drug (varying by plan) and it is not clear how such a system would move such differently priced drugs through the supply chain. It also may have significant implications for “best price” rule payments by manufacturers to State Medicaid plans.

Discussion

There is no perfect solution that eliminates all the challenges created by rebates while leaving payers with a similar level of negotiating leverage to help moderate costs. Forcing an abrupt transition away from rebates would raise significant questions about the impact on total costs of care and on patient access and outcomes. Even small increases in health care insurance premiums might have significant effects on individuals who already struggle to afford health insurance for drugs through their employer, health insurance exchange, or Medicare. Any effort at rebate reform should therefore realize the broad effects and the potential for unintended consequences.

Nonetheless, nearly all stakeholders in the health care system realize that some form of change to the current paradigm of rebates is needed, and the market is already moving toward 100% rebate pass-through. Early efforts at establishing a POS rebate model to help patients reap the benefits of negotiated prices are also now in play, although it is too early to evaluate the outcomes. Nonetheless, an aspirational target of moving fully toward a system in which upfront discounts were part of a broader transformation in drug negotiation and delivery is shared by a surprising number of stakeholders. A future health care system whose incentives are fully aligned toward rewarding value while improving access and outcomes for patients will require more radical change than simply giving patients part of the rebate at the POS. We hope this white paper will chasten policymakers who might have seen eliminating rebates or any of the other options as an easy, clean procedure. We equally hope that it will hearten and inform those who wish to take a thoughtful, careful approach to near-term reform while laying the groundwork for a greater transformation to come.

1. Introduction

1.1. Context

As pharmaceutical spending has risen in the US, health plan sponsors, insurers, and Pharmacy Benefit Managers (PBMs) have faced increasing challenges to maintain affordability. Among the mechanisms that have been implemented to try to control overall costs, health insurance benefit designs based on high initial deductibles and co-insurance within a tiered drug formulary have been effective, but have placed ever greater financial burdens on patients, especially those who require expensive on-going treatment for chronic conditions. The combination of rising drug costs at the system level and increasing financial stress for individual patients has triggered intense national concern.^{1,2} Policy makers across the political spectrum are eager to find root causes, highlight unfair market practices, and find solutions that can control drug costs and improve patient access and affordability.

As policy solutions have been sought, one target has come under increasing scrutiny: rebates. Rebates are a staple of negotiations between pharmaceutical companies and payer organizations (which we define as including health insurers and PBMs) and represent a *quid pro quo*: discounts to the list price of drugs (rendered post-sale as rebates) are offered in exchange for preferential formulary placement. Concern about drug prices initially brought negative attention to the role played by drug makers in setting and raising prices, but soon the focus was expanded to include the role that “middlemen” such as PBMs played in rebate negotiations.^{3,4} The claim against PBMs is that a substantial part of their revenue has traditionally come from keeping a percent of the absolute rebate amount they can negotiate, thereby creating a pernicious incentive to favor higher list prices from which a larger rebate can be obtained. Although the net price to insurers and plan sponsors might not change if increases in list prices are matched by correspondingly larger rebates, patients face the full impact of higher list prices since it is to these prices that benefit designs link out-of-pocket requirements. Rebates have therefore rapidly become an extremely contentious topic, still praised by many as the best tool available to provide competitive leverage for payers seeking lower net prices, but reviled by others who view it as the chief sin in a system that punishes sick patients with higher out-of-pocket costs and absorbs billions of dollars that could otherwise either reward innovation or keep costs down, or both.⁵

Some stakeholders have also noted that rebates can warp the competitive landscape for new drugs trying to compete with existing drugs that have broader indications and significant market share, allowing their manufacturers to offer far more substantial rebates to PBMs and payers.⁶⁻⁸ For example, in crowded drug classes such as autoimmune therapies, some drug makers have contended that new drugs with only a single indication, including some biosimilars, cannot get preferable formulary placement over existing leading drugs, even when new drugs are shown to offer better outcomes at a lower price, because the older drugs have multiple indications and billions of dollars of sales, generating rebates that are so substantial that payers would lose money by switching to the more cost-effective options for a single indication.⁹

Given these concerns, calls for reform of the rebate system have multiplied. In 2018 the Trump administration made clear its own dissatisfaction with the current rebate system and sought public comments on options for alternative models.¹⁰ While still considering public comment, in July 2018, the Trump administration moved forward and submitted a proposed draft rule to the Office of Management and Budget (OMB) to scale back legal protections that allow rebates within federal insurance systems without triggering anti-kickback provisions.¹¹ The proposed rule, whose provisions remain unknown at this time while awaiting approval by the Office of Management and Budget, have raised speculation that major changes will be introduced in the allowed scope and nature of rebates.¹²

Private companies have also responded to the rapidly evolving policy debate targeting rebates. In September 2018, Gilead announced that it would launch authorized generics of its two best selling drugs for Hepatitis C – Epclusa® and Harvoni® – with steep discounts of 68% and 62% off of their list prices for a course of treatment.¹³ Payers will now be able to choose between the discounted authorized generic and the full-price rebated drug. In October 2018, Amgen announced they would lower the list price of their cholesterol drug, Repatha, by 60% in lieu of seeking a similar net price through steep rebates.¹⁴ To capitalize on these moves by drug makers, and to lay the groundwork for further private market action to reduce the role of rebates, Express Scripts announced that it would offer a new “Flex” formulary option in 2019 to allow plan sponsors to select options with lower list prices and no rebates over options of the same drugs paid at a higher list price and corresponding rebate. Express Scripts said its explicit goal was to offer formulary designs that can ‘reduce reliance on rebated brand products.’¹⁵

With action within the federal government and the private market, the US thus appears poised for dramatic changes to a fundamental part of the drug pricing and coverage landscape. But what is known about how the rebate system interacts with other elements of drug pricing, coverage and delivery? And, for different stakeholders, what are the potential benefits and possible negative consequences of realistic possible alternatives? This White Paper, benefitting from interviews with numerous participants in the rebate process – from plan sponsors, to insurers, to PBMs, to drug makers – seeks to address these questions and to lay out a framework for evaluating proposed alternatives to a rebate model that has served as the cornerstone of drug pricing and coverage negotiation for decades.

1.2. Our Approach

This White Paper is structured to provide first an overview of the development of the current rebate system (section 1); describe how rebates flow between manufacturers, payers, and patients (section 2); explore what impact rebates have on key stakeholders in the health care system (section 3); outline two key aspects for consideration of reform (section 4); and analyze the potential consequences of alternatives that might replace the current rebate model (section 5). We conclude in section 6 with an analysis of key policy perspectives to guide future consideration of alternative rebate models, before offering a final discussion of the issues in section 7.

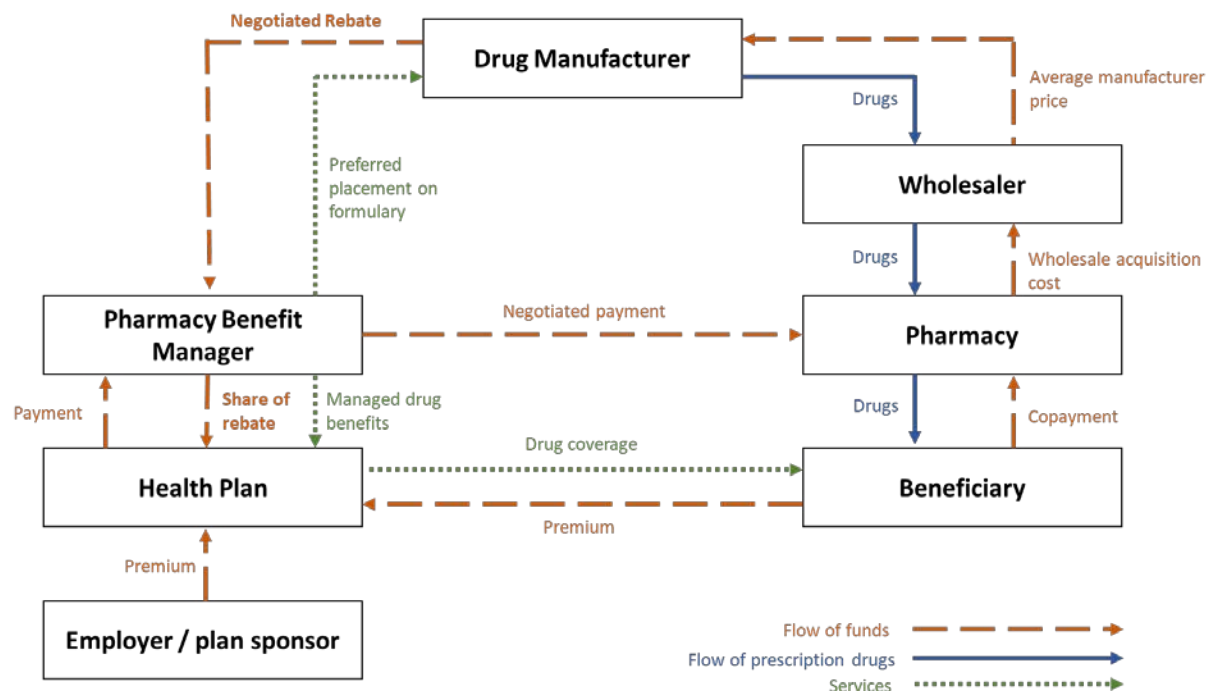
In preparing the paper we undertook a focused literature review and evaluated the written responses to the HHS Blueprint on drug pricing from key stakeholders, including all participants in the ICER membership program. We also conducted ten interviews covering PBMs, public and private payers, manufacturers, academics, benefit consultants, and trade associations. An earlier version of this paper was sent out as a pre-read for the ICER members Policy Summit. This version of the paper takes account of the discussion at that meeting.

Throughout this paper we describe how all alternatives to the current rebate system offer potential risks or disadvantages as well as potential benefits, and that the implementation of any major reform may pose daunting practical challenges given the multitude of ways that rebates affect various parties within the drug delivery chain. We outline the evidence presented to date, and the key questions that still need to be answered. Like an operation deep inside the brain, extracting the current rebate system and implanting something new would require careful attention to intricate structures, a steady hand, and very precise interventions in order for the patient to ultimately emerge safe and improved.

1.3. How do rebates work?

The supply chain for pharmaceuticals in the U.S. is complex, involving many different stakeholders with competing interests. Sood et al.¹⁶ calculate that 41% of prescription drug expenditure accrues toward intermediaries in the pharmaceutical distribution system. The following figure illustrates the flow of services, products, and payments (including rebates).

Figure 1.1. Simplified illustration of the flow of products, payments and services in the pharmaceutical supply chain



Source: Illustration based on Congressional Budget Office¹⁷

Rebates are negotiated between drug makers and payers (insurers or PBMs) when drugs first enter the market and can be renegotiated on a regular or ad hoc basis. As mentioned earlier, rebates are used as an element of negotiating favorable placement within a drug formulary. For example, a company desiring its drug to be placed in a best tier of formulary, in which the drug can be considered a “preferred” drug for clinicians, with more limited drug management and low out-of-pocket payments required from patients, may offer a larger rebate off the announced list price.

Rebates are thus more common and usually larger in drug areas in which there is significant competition, especially when competition is among drugs with similar mechanisms of action and only incremental, if any, differences in clinical risks or benefits. Drug areas with substantial rebates include drugs for diabetes and autoimmune agents used for conditions such as rheumatoid arthritis and psoriasis.

Although rebate levels are negotiated “upfront” before the drugs are prescribed, they are not implemented as discounts on the initial price paid, either by the payer or by the patient. Instead, rebates are paid retroactively, and may include a sliding scale based on the volume of prescriptions or market share. In other words. The rebate will be greater, i.e. a lower net cost, if the number of prescriptions is higher, reflecting a trade-off between net price and volume. Where relevant, PBMs share all or some portion of rebates with the health insurer or the plan sponsor based on their contractual agreement.

Manufacturers say that they can offer larger rebates if they increase their list prices. However, as discussed in Section 1.5, the relationship between list price trends and trends in rebates is not straightforward.

1.4. History of the Transition from Discounts to Rebates

Historically, PBMs competed by negotiating terms with pharmacy networks, managing the delivery of specialized pharmaceutical products, and processing prescription transactions (claims) on behalf of health plans. The role of PBMs has expanded from claims processing, to the development of formulary management, which has coincided with their exercising of market power to negotiate with drug manufacturers to encourage competition on prices in drug categories where there are multi-source products or several on-patent products competing in a therapeutic area.

Prior to 1996, manufacturers offered discounts to health plans for their drugs, while charging an undiscounted list price to wholesalers and pharmacies. Wholesalers would then bill the manufacturer for the difference between the amount they purchased the drug for from the drug manufacturer, and the amount they were reimbursed by the pharmacy as determined by the health plan. Pharmacies, however, had no direct relationship with the drug manufacturer and could not reconcile their payment; so, while they paid full retail price for the drug to the wholesaler (plus a wholesaler markup), they were only reimbursed for the amount as determined by the health plan based on a negotiated rate with the drug manufacturer. Despite attempts by pharmacies to cut out wholesalers and collectively bargain with drug manufacturers to obtain more competitive rates, none were offered.

In 1996, a class action lawsuit was brought by retail pharmacies against major drug manufacturers alleging that they had violated the Sherman Antitrust Act and were hampering competition by negotiating upfront price discounts only with payers, and not with independent and chain pharmacies.¹⁸ The outcome of this lawsuit saw manufacturers enter into a court-approved settlement in which they agreed that they would (1) not refuse to discount goods based solely on the status of the buyer entity and (2) offer the same types of discounts previously reserved for plans to pharmacies and retail buying groups that could demonstrate an ability to affect market share in the same manner.¹⁸ As a result, manufacturers restructured their contracts with payers based on retroactive rebates tied to prescription volume and market share rather than upfront discounts. Pharmacies would be paid by payers for the drug at the price at which it was obtained from the wholesaler plus any supply chain markups. And payers would then receive any retroactive rebate direct from the drug manufacturer.

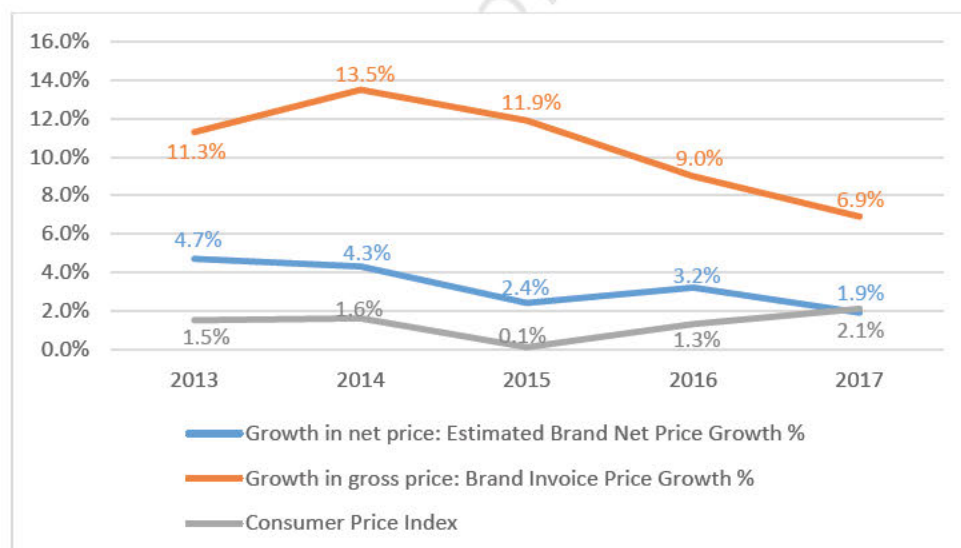
In reaction to this evolving landscape toward rebates and away from upfront discounts, the Office of the inspector General at HHS issued a “safe harbor” protection in the late 1990s to shield drug companies’ rebate contracts from the implications of the Anti-Kickback Statute (AKS). The AKS prohibits remuneration for referrals or services that are payable by a federal program (i.e. Medicare) - in effect paying someone to recommend your product under a federal health care program.¹⁹ In place since 1971, this safe harbor provision is now being questioned by HHS. Its revocation by the federal government could serve as a powerful tool to reshape the discount/rebate structure in federal health programs with knock-on implications for private sector health insurance markets.

1.5. Perspectives on the “Gross-to-Net” Price Gap

Opinions on the magnitude of the difference between list prices and net prices following rebates, and the role that rebates play in driving overall drug expenditures, are highly contentious across different stakeholders and commentators. Manufacturers say that they can offer larger rebates if they increase their list prices, which is supported by some analyses linking increased overall spending on rebates with increasing list price trends.²⁰ However, studies commissioned by the Pharmaceutical Care Management Association (PCMA) and the America’s Health Insurance Plans (AHIP) demonstrate no positive relationship between list price levels and the amount obtained in rebates for specific drugs and drug classes.^{20,21}

There is general agreement that the gap between list price and net price is widening as a cumulative sum: over the five years between 2012 and 2016 the total value of pharmaceutical manufacturers’ off-invoice rebates and other price concessions more than doubled from \$59 billion to \$127 billion.^{22,23} IQVIA has shown that invoice price growth (i.e. gross price) has continually out-paced net price growth (which accounts for rebates), and both have been above inflation (with the exception of net price growth in 2017); this is shown in Figure 1.2.

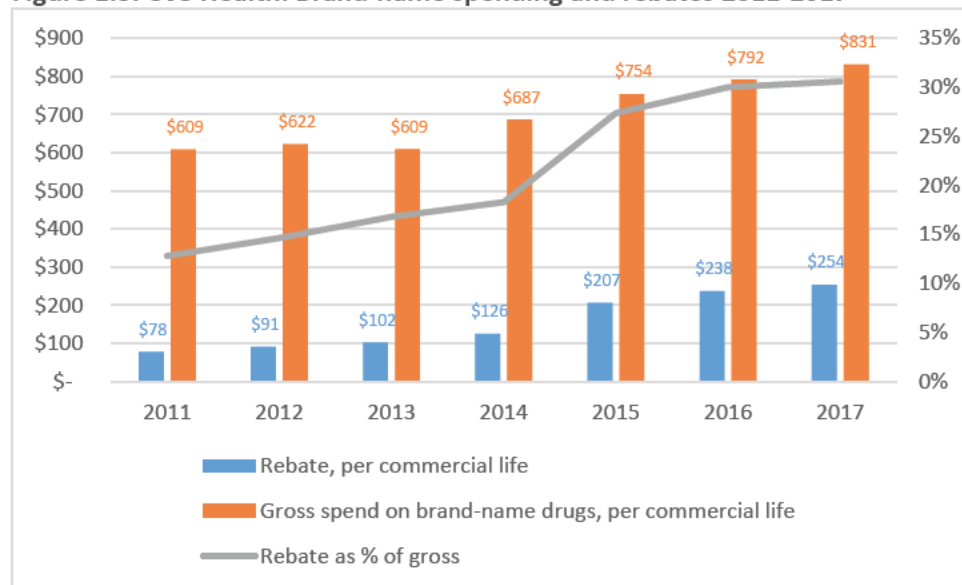
Figure 1.2. IQVIA data on protected^a brands gross and net price growth 2013-2017



Source: Data from IQVIA²²

Data from the Office of the Inspector General (OIG) and CVS corroborate this growing gap between list price and net price.^{24,25} In a 2018 report, OIG demonstrates that while reimbursement for Medicare Part D increased 62% from 2011 to 2015 (\$49 billion to \$80 billion), rebates more than doubled (\$9 billion to \$23 billion) over the same timeframe.²⁴ CVS data also demonstrate that whilst gross expenditure on brand-name drugs has increased, the corresponding level of rebate has increased faster, leading to a higher proportion of gross expenditures being rebated from 13% in 2011 to 31% in 2017; this is represented in Figure 1.3.

Figure 1.3. CVS Health: Brand-name spending and rebates 2011-2017



Source: Data from CVS Health²⁵

For patients, the gap between list and net price can substantially affect out-of-pocket spending at the pharmacy counter. In the past decade, employers and individuals have shifted toward benefit designs with high out-of-pocket cost structures, including deductibles, co-insurance, and tiered formulary design. Patients' out-of-pocket expenditure has been linked to list prices instead of net prices since net prices are considered proprietary and are only determined retroactively. A large gap between list and net price therefore matters to patients, who, in some cases, might pay more out-of-pocket for the drug than its actual true (net) cost to the plan.²⁶ Examples of patients paying high out-of-pocket costs, without benefiting from the rebates negotiated for a therapy, have become commonplace in mainstream news throughout the past several years, including high profile stories about insulin and the EpiPen.^{27,28}

^a Protected brands are products that have been on the market two years or more and have yet to reach patent expiry.

2. Rebates in Different Insurance Markets

The size of rebates on branded drugs vary across public and private insurance carriers. Werble et al. estimated that negotiated rebates are, on average, approximately 30% of the list (WAC) price.²⁹ Roehrig found that Medicare Part D plans achieve higher average rebates (31%) than private plans (16%),²⁸ and Medicaid, where state governments have the additional leverage of the “best price” rule, receives the highest average rebates on branded drugs (61%). Rebates also differ by drug types; a study of Medicare Part D rebates found that rebates were highest for drugs with brand competition (average 39% of gross cost), while protected class drugs^b had lower average rebates: 14%.³⁰

A 2016 study commissioned by the PCMA estimated that “from 2016 to 2025 the current use of PBM tools in the market place will save plan sponsors and consumers approximately \$654 billion.” The authors break this down by plan type: \$350 billion for commercial plan sponsors and their members, \$257 billion for Medicare Part D, and \$48 billion for Medicaid.³¹ In Table 2.1, below, we summarize the main characteristics of the different types of plan and how rebates work within each.

^b There are six protected classes (anticonvulsants, antidepressants, antineoplastics (including many oral chemotherapy drugs), antipsychotics, antiretrovirals, and immunosuppressants. Part D plans to cover “all or substantially all drugs” within each of the classes.

Table 2.1. How rebates work in different insurance schemes

	Medicaid	Medicare Part D	Medicare Part B	Private insurance (for comparison purposes)
Total drug expenditures ^{a,b}	\$62 billion	\$142 billion	\$26 billion	\$194 billion
Estimated rebate achieved off list price for brand name drugs ^c	61%	31%	No incentive to provide rebates and no estimate identified in the literature.	16%
Who are rebates negotiated by?	Innovators must provide a rebate of 23.1% of AMP ^d , or the manufacturer's "best price", whichever is greater. Supplemental rebates are negotiated by State Agencies (or PBMS on their behalf)	Commercial Plans (who often use PBMs)	Medicare pays providers ASP ^e + 6%	Commercial Plans (who often use PBMs)
How do rebate negotiations impact access for patients?	Status on Preferred Drug List	Drug management (Tiers, Prior Authorization, Exclusions) and cost sharing	Not applicable	Drug management (Tiers, Prior Authorization, Exclusions) and cost sharing
Where do savings from rebates go?	Medicaid / state	Reduced premiums (and therefore reduced government subsidies). Possible % retention by PBMs depending on arrangement, but all payment adjustments after the point-of-sale (including rebates) must be reported and given back 100% to CMS ^c .	Medicare	Reduced premiums and in some cases, reduced patient out-of-pocket costs. Possible % retention by PBMs depending on arrangement

^a Source: Roehrig³² for Medicaid, Medicare Part D and Private insurance. Reference year 2016, and represents total spend at the point of purchase, i.e. *prior to rebates* (\$).

^b Source: MedPAC³³ for Medicare Part B. Reference year 2015, and represents total spend on drugs and biologics based on average sales price (*accounts for rebates*)+6%

^c Source: Roehrig.³² Note these represent rebates achieved for brand name drugs. Estimated rebate for total point of sale drug spend (i.e. including generics) was 51%, 22% and 12% respectively.

^dAverage Manufacturer Price (AMP): Average price paid by wholesalers to manufacturers for drugs sold to retail pharmacy.

^eAverage Sales Price (ASP): Average price realized by a manufacturer to all purchasers, net of rebates, discounts and price concessions. Note: does not account for all rebates under the Medicaid program. Source: MedPAC.³³

2.1. Medicaid

Because of the Medicaid Best Price rule, introduced in the Omnibus Budget Reconciliation Act of 1990, Medicaid programs across the country obtain either (a) a minimum rebate of 23.1% off the average manufacturer price (AMP) for branded drugs or (b) the “best price” offered to any other public or private purchaser (whichever is the higher discount). The intent of this rule is to enable the public sector to get the benefits of private sector bargaining power and ensure the Medicaid program is not paying more than the private sector for its drugs.³⁴ In turn, Medicaid programs must cover all prescription drugs (with some exceptions).

State based Medicaid programs can negotiate deeper, “supplemental” rebates themselves or through a PBM. These negotiations are on a state-by-state basis, or sometimes achieved through cooperatives of states collectively bargaining on drug prices. State negotiated supplemental rebates can be applied to drugs purchased by all Medicaid managed care organizations contracted through the state. The impact of rebates on out-of-pocket costs for patients is not an issue in Medicaid, as beneficiaries have very low cost-sharing, which is often fixed and not related to drug cost. However, in order to incentivize negotiations for supplemental rebates, states can put therapies on a preferred drug list to streamline access for their members without drug management requirements.

Depending on the state Medicaid program, an important feature may be that rebates can be used to cross-subsidize other state spending. Given that Medicaid programs obtain substantial rebates, some PBMs believe that this revenue stream is so important to states that it reduces their interest in eliminating rebates.

There are several factors that contribute to the high rebate rates that are achieved under the Medicaid program. One is that manufacturers who refuse to participate in Medicaid are excluded by law from Medicare (which represents a much larger market share for prescription drugs). In addition, the government requires that Medicaid receive a minimum of 13% of AMP rebate on generic drugs.³² Between 2006 and 2009, the Office of the Inspector General (OIG) found that Medicaid recouped through rebates between 29% and 38% of its prescription drug expenditures each year, resulting in an average annual savings of about \$8 billion. These arise both from the best price rule and an additional rebate based on an inflationary component if the increase in a drug’s AMP exceeds the increase in the Consumer Price Index.

Private payers argue that the Best Price Rule sets an artificial floor for their negotiations, limiting their ability to negotiate rebates deeper than 23%. Soon after the creation of the Medicaid Drug Rebate Program (along with its ‘best price’ principle), payers viewed increased prices in the commercial sector as an effort by manufacturers to offset losses in the Medicaid program or to avoid “resetting” their best price. Both Congress and HHS have tried to address this effect by excluding certain prices, discounts, and rebates from the definition of AMP and best price.³⁵

^c There is a “risk corridor” within which plans can keep some additional revenues from rebates.

2.2. Medicare

There is no rebate program for Medicare Part B drugs. Rather, providers are paid the average sales price (ASP) plus 6%. The ASP is net of all rebates and price concessions, and therefore the program benefits indirectly from the rebates achieved by the rest of the market. In 2013 the OIG was asked to calculate the potential savings for Medicare if a rebate program similar to that of Medicaid (basic rebates and inflation-indexed rebates) were applied to Medicare Part B drugs; they estimated that savings of around 20% or more (\$2.7 to \$3.1 billion) could be realized, but that there were several implementation issues related to claims and data that would need to be addressed.³⁶ After receiving a Congressional request, the OIG conducted another analysis in 2017 that estimated savings of \$1.4 to \$1.8 billion could be realized for Part B drugs if inflation-indexed rebates accorded Medicaid were extended to Part B.³⁷

Under Medicare Part D, private insurers negotiate rebates with manufacturers independently with no government involvement, but all savings must be reported and paid to the government.^d As demonstrated in Table 2.1, Medicare Part D drugs obtain high rebates compared with those covered by private insurance. This is believed due to “the wider use of utilization management and multi-tiered and exclusionary formularies in Medicare Part D than in commercial plans [which] creates a greater risk/reward for the exclusion or inclusion of a manufacturer’s brand and encourages greater concessions through competitive forces.”³⁸ In addition, Medicare Part D beneficiaries are more sensitive to premium levels since many are on fixed incomes, and are therefore more likely to accept a restrictive formulary, enhancing the bargaining power of Part D plans.³²

While higher rebates in Part D compared to the commercial market may help moderate premium growth, cost-sharing for Part D patients is linked, as it is for commercially insured patients, to the list price. However, Medicare Part D has reinsurance for high cost patients who have over \$8,500 in estimated out-of-pocket drug costs. After this “catastrophic” threshold is met, the government picks up 80% of the bill, Part D plan liability is just 15%, with the remaining 5% paid by patients.^{39,40} A number of commentators have highlighted that this shift in financial responsibility at the catastrophic threshold gives PBMs and Part D plans an incentive to favor high-cost high-rebate drugs as high list prices push beneficiaries into the catastrophic phase more quickly, as the compulsory discount manufacturers are required to give patients is included in the patient cost calculation when determining whether the \$8500 threshold is reached.

The end effect has been that the share of the overall cost that Part D plans pay is decreasing as high-price, high-rebate arrangements increase. According to Antos and Capretta,³⁹ the government spent \$37 billion in 2017 covering expenses for beneficiaries above the catastrophic threshold, which was \$9 billion (about 25%) higher than in 2008. In line with this cost growth, the Medicare reinsurance subsidy (on a per member-per year basis) grew at an annual rate of nearly 17% between 2010 and 2015.⁴⁰ CMS policy makers have concluded that “Under current rules, Part D sponsors may have weak incentives, and, in some cases even, no incentive, to lower prices at the point of sale or to choose lower net cost alternatives to high cost-highly rebated drugs when available.”⁴¹

^d As noted in the footnote to Table 2.1 there is an exception for the risk corridor.

2.3. Commercial Markets

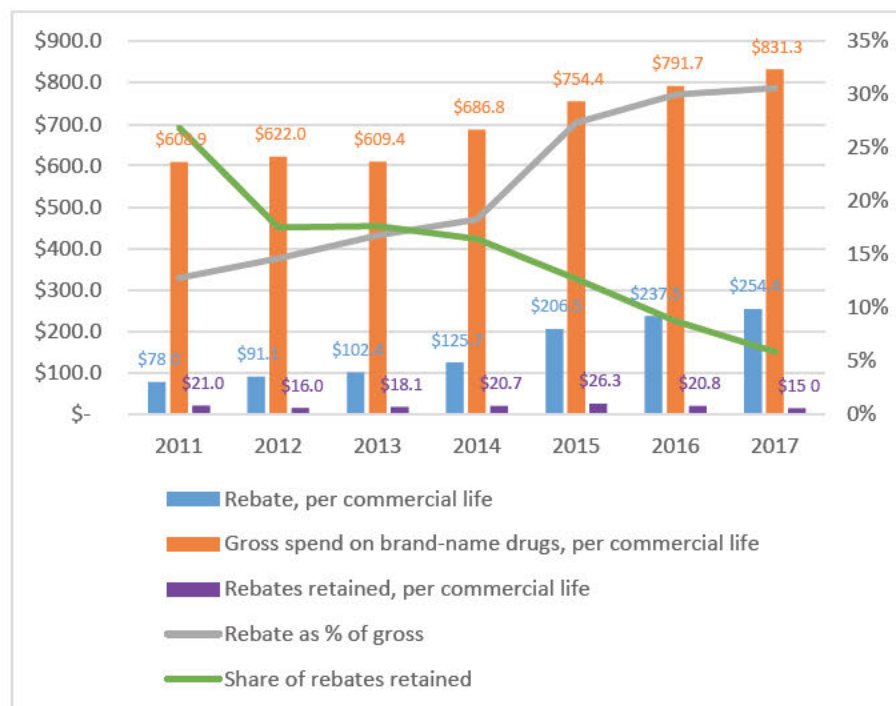
Flow of rebates from PBMs to payers

The contractual relationships between PBMs and payers take many different forms. As part of these contracts, PBMs often retain a percentage of rebates, although a growing number of payers are now seeking contracts in which all rebates are returned to the payer, often called a rebate “pass-through.”⁴² In some cases, PBMs offer a contract with a guaranteed level of rebate to the payer, an arrangement which subjects the PBM to more risk but offers the payer a predictable cash flow.²⁵

The percent and absolute amount of rebates retained by PBMs has been evaluated by different groups. A survey report from the Pharmacy Benefit Management Institute (PBMI) reported that just under half of employer respondents said they received 100% of rebates (either with a minimum rebate guarantee [27%] or without [22%]), a significantly higher percentage than similar estimates from 2014.⁴³ A recent study by Visante on behalf of PCMA states that, on average, around 90% of rebates are passed through to payers.²¹ Cumulatively, Roehrig finds that in 2016, \$89 billion in rebates were paid to health insurers, reducing total retail drug spending by 21%.³² This same study estimates total PBM profits to be \$11 billion and suggests that the notion that PBMs divert a large share of rebates to excess profits is not supported by the data.

Statements by two large PBMs – CVS and Express Scripts – also suggest that rebate retention is no longer a significant part of their business model. Data that CVS has published shows a downward trend in rebate retention over time.²⁵ Figure 2.1 illustrates the amounts in rebates obtained and retained by CVS from 2011 to 2017.

Figure 2.1. CVS Health: Brand-name spending, rebates and rebate retention 2011-2017



Source: Data from CVS Health²⁵

It can be observed from the Figure above that whilst rebates over time have increased substantially (from 13% of gross spend in 2011 to 31% in 2017), the share of those rebates retained by CVS has declined, from 27% in 2011 to just 6% in 2017. According to CVS, in the first half of 2018 CVS Caremark retained just 2% of rebates.²⁵ Similarly, Express Scripts states that they pass on 95% of rebates, and that nearly half of their clients opt for 100% pass-through of rebates.⁴⁴ The implication is that PBMs are shifting to charge for more of their services in other ways than taking a share of rebates.

Flow of rebates from PBMs and payers to patients

A 2017 PBMI report asked plan sponsors how rebates are used: 68% indicated that rebates are used to reduce plan spend on drug costs, whereas only 4% of plan sponsors were using rebates to reduce member out-of-pocket costs at the point of sale (POS). PhRMA and others critical of the lack of a POS rebate system for patients refer to this as “reverse insurance” in which those who need medications are required to pay more than others.^{45,8} It should be noted that some insurers, including major national carriers UnitedHealth Group and Aetna, have recently announced the introduction of POS rebate benefit designs.^{46,50}

3. How do rebates impact different stakeholders?

3.1. Empirical studies on the impact of rebates

There are a small number of empirical studies that consider the relationship between list price and rebate levels. They are as follows:

- A report by Milliman prepared for America's Health Insurance Plans (AHIP). This provides an analysis of historical Medicare Part D drug prices and manufacturer rebates. The report finds that brand drugs with rebates have higher historical list price trends than brand drugs without rebates.²⁰ However, among drugs with rebates, there is no difference in historical list price trends between drugs with higher rebates and those with lower rebates. In addition, the highest cost branded drugs have, on average, the lowest manufacturer rebates. The analysis does not analyze or hypothesize any causation for these relationships. What seems clear from the data is the impact of competition on rebates. More competition leads to higher rebates. However, this is not necessarily the same as lower net prices.
- CVS Health offers a response to what it describes as the "myth" about a positive relationship between rebate size and list price.²⁵ Its report, published in August 2018, argues that if this were the case, there would be a strong correlation between rebates and list prices. On the contrary, the report compares list price increases (2015 to 2018) with average rebates for six specific drug categories, showing that list price increases are higher for drugs with smaller rebates. According to the analysis, list prices for anticonvulsants and multiple sclerosis drugs rose over the time period by 46% and 27% respectively, while annual rebates were only 6% and 7%.^{25,47} However, the authors do not explain how the six drug categories were selected. Finally, they do not explore how list price increases might relate to changes to rebates over time. These explanations are important to differentiate between (1) therapy areas with only one or two manufacturers, where we might expect to see high prices, high price increases, and low rebates; and (2) competitive areas where we might see high list prices, high price increases, and high discounts.
- A report by Visante on behalf of PCMA similarly argues that there is no correlation between rebate levels and price increases by manufacturers.²¹ The authors' analysis suggests that among the top 200 brand drugs, there is no correlation between average rebate levels negotiated with PBMs and increasing prices set by manufacturers. Furthermore, they suggest that manufacturers raise prices even when rebates are low. This is consistent with the hypothesis that there are two different types of market: those where manufacturers have strong market power and those where there is a lot of competition.

- A 2016 Bloomberg analysis illustrates examples of the increasing divergence between list and net prices at the product level.⁴⁸ In a study of 39 products with global sales above \$1 billion per year, looking at the six-year period Q4 2009 to Q4 2015, they found that net prices after rebates increased at nearly the same rate as CPI inflation for 12 products (31%); for the other 27 products (69%), net prices rose well above inflation. For 31 of the products (79%), the percentage gap between list price and net price rose over the period. For the remaining eight (21%) it fell.

3.2. Rebates and the Flow of Revenue Within the Pharmacy Supply and Financing System

Given the number of parties involved in the pharmaceutical distribution and financing chain, and the confidential nature of the contractual arrangements between them, the flow of money is difficult to track. Two reports attempt to do so. Sood et al.¹⁶ look at the gross and net profit data of large publicly traded companies in this distribution chain. Their analysis demonstrates that for every \$100 spent in retail pharmacies, around \$17 compensates direct production costs, \$41 accrues to the manufacturer (\$15 of which is net profit), and the same amount (\$41) accrues to intermediaries: wholesalers, pharmacies, PBMs and insurers (with \$8 of net profit split among them). A study performed by the Berkley Research Group, sponsored by PhRMA, found that brand manufacturers captured 39% of initial gross drug expenditures; and 42% is captured by non-manufacturer entities.⁴⁹ In their analysis, wholesalers and pharmacies realized 22% of total drug spending; and payers and PBMs realized 20% of total drug spending.

3.3. Public Comments on Rebate System Alternatives from Different Stakeholders

The viewpoints of various stakeholders on the relative benefits and negative consequences of the current rebate system are understandably different. We reviewed the public comments submitted to HHS in response to its request for input. Table 3.1 summarizes the views of organizations participating in the ICER membership program, along with statements from major trade associations who responded directly to the HHS Blueprint. Our summary of the viewpoints is supplemented by information gained from telephone interviews undertaken with representatives of the key stakeholders.

Table 3.1. ICER Membership summary of comments to the HHS Blueprint

21/29 ICER Members submitted comments to HHS blueprint;
Also included are comments submitted by PhRMA, BIO, PCMA, and the Campaign for Affordable Rx Pricing Payers (<i>Anthem, HCSC, Aetna, AHIP, Cambia Health Services, United, Kaiser</i>) were most likely to:
○ Oppose prohibiting rebates (86%);
○ Support reforming Medicaid best price rule because of its impact on negotiating rebates (86%);
○ Oppose requiring point of sale rebates (86%).
PBMs (<i>CVS, Express Scripts, and PCMA</i>) were most likely to:
○ Oppose prohibiting rebates (100%);
○ Oppose fixed price discounts (100%);
○ Support reforming Medicaid best price rule because of its impact on negotiating rebates (66%);
○ Support confidentiality (66%).
Pharmaceutical Companies (<i>Biogen, NPC, Genentech, GSK, Mallinckrodt, Merck Inc, Novartis, Regeneron, Sanofi, Alnylam, Astra Zeneca, Johnson and Johnson, PhRMA, BIO</i>) were most likely to:
○ Support Point of Sale rebates (71% Agree);
○ Were split on prohibiting rebates (36% yes; 21% no; 7% on the fence; 36% did not state);
○ Support confidentiality (14%).

4. Key aspects for consideration of reform

Before outlining the major policy alternatives to the current rebate system, in this section we highlight two important characteristics that should be carefully considered in weighing the pros and cons of any potential future model. These are: 1) transparency; and 2) the ability to administer outcome-based contracts. We introduce these topics in this section and elaborate where relevant within the discussion of the specific policy options in the next section. Both themes also appear in the major “criteria” that we propose for assessing policy options.

4.1. Transparency of Rebate Amounts

The desirability of transparency is contested by many stakeholders, both in responses to the HHS Blueprint and in other statements. Transparency of rebate amounts at the individual drug level is viewed by many as a direct outcome of eliminating rebates and moving to an upfront discount model. With other approaches in which rebates are retained in some fashion, transparency is more often viewed as optional, something that can be accommodated or that can be avoided.

Full price transparency throughout the drug delivery chain is seen by some as the only way for plan sponsors and insurers to fully understand the outcomes of their contractual relationship with PBMs and to ensure that rebates are flowing back to payers as intended. Similarly, it is argued that transparency of rebates and all other fees from manufacturers would limit the incentives of PBMs to include certain drugs in the formulary that generate more revenue for the PBM but which are not the most cost-effective for the payer. Transparency of rebates for the patient at the point of sale is held out as one way to increase pressure on payers and PBMs to share those rebates with patients.

In contrast, many others have argued that too much transparency could lead to higher net prices for two reasons. The first is that it could degrade the ability of manufacturers to offer larger rebates to certain payers. If all payers and PBMs know what the “best” rebate is in the marketplace, all would be able to seek it. As a response, manufacturers would be likely to calculate the most profitable *uniform* level of discount across all payers, which might result in higher net prices overall.

Second, some commentators worry that transparency could even lead to tacit collusion by competing manufacturers. The PCMA highlights in its response to the HHS Blueprint that the Federal Trade Commission (FTC) itself has stated that, “[i]f pharmaceutical manufacturers learn the exact amount of rebates offered by their competitors ... then tacit collusion among manufacturers is more feasible ... Whenever competitors know the actual prices charged by other firms, tacit collusion — and thus higher prices — may be more likely.”⁵⁰ CVS supports this point of view, reiterating that the Congressional Budget Office (CBO), FTC, and CMS have all expressed concerns regarding the competitive effects of disclosing drug-specific rebate data. The CBO has stated that the disclosure of rebates could impact Medicare spending for a number of medical conditions where there are only a few drugs available and thus the “disclosure of drug-by-drug rebate data in those cases would facilitate tacit collusion among those manufacturers, which would tend to raise drug prices.”⁵¹

4.2. Maintaining the possibility of implementing outcome-based contracts

Outcomes-based contracts, sometimes called “value-based contracts,” have become more common over the past decade. These contracts between drug manufacturers and payers feature increased rebates to payers if pre-specified clinical or economic outcomes are not achieved with treatment. For example, Harvard Pilgrim Health Care has announced outcomes-based based contracts with Amgen in which increased rebates for Amgen’s PCSK9 cholesterol drug are paid back to the insurer when the protective effect of the drug fails to prevent a heart attack or stroke.⁵² Whilst some commentators argue that the evidence is not convincing that outcomes-based contracts make an impact on cost or quality of care,⁵³ manufacturers, payers and policymakers (including the Trump administration) have identified outcomes-based contracts as one important mechanism for linking the overall payment for drugs to the value of the clinical outcomes they achieve.

It is important to note that outcome-based contracting cannot be viewed as a “solution” to the problems arising from rebates. It is likely to be limited to a very small number of drugs, and links to outcomes alone do not address concerns about highly price drugs at market entry. But given the general desire to facilitate further experimentation with outcomes-based contracts, consideration should be given to designing options to the current rebate model that will protect and, if possible, promote these efforts. They offer payers a mechanism to address uncertainty and to share risk that is inherent to the transition of drugs from a controlled clinical trial setting to the real-world.

5. What are the alternative options for rebate models?

Many different alternatives have been put forward by critics of the current rebate system. The major options, however, can be separated into two categories: 1) those that retain retroactive rebates but have some requirements to channel rebates back to payers and patients in prescribed ways; and 2) an alternative model that eliminates retroactive rebates entirely, replacing the current structure with upfront discounts. For shorthand, the first set of alternatives can be labeled as ways to “reform rebates” while the second moves formally to a system that “replaces rebates.” The two options to reform rebates could be implemented as stand-alone options or combined. In addition, all of the alternative rebate models can be implemented with varying degrees of transparency regarding the rebate/discount amount, but upfront discounts would most likely force transparency at the individual drug level, given that any linkage of patient payment to the discounted price would allow other stakeholders to gain knowledge of the discount.

The alternative options are portrayed below in Figure 5.1 and consist of:

- **Option 1:** Retain rebates with a requirement that PBMs pass on 100% of manufacturer rebates and fees to the plan sponsor.
- **Option 2:** Retain rebates with a requirement for point-of-sale (POS) rebates to patients.
- **Option 3:** Eliminate rebates in favor of a return to upfront discounts.

Table 5.1. Alternatives to the current rebate system

Reform Rebates	Replace Rebates
<ol style="list-style-type: none">1. 100% pass-through of rebates2. Point of Sale (POS) rebates applied to patient out-of-pocket cost sharing	<ol style="list-style-type: none">1. Eliminate rebates and move to upfront discounts

In the sections below, we describe each of these alternative options in greater detail. We also analyze their respective advantages and disadvantages, including practical considerations in their implementation. As noted earlier, both rebate reform options could be linked or could be implemented separately so we address them separately in the section below.

We begin by setting out possible criteria by which the different options could be judged and then, after discussing the options, we summarize the advantages and disadvantages in a Table.

5.1. Major Considerations for Alternative Rebate Models

We have focused on the following criteria by which the various alternatives can be evaluated:

- Impact on patients' affordability, access to care, and clinical outcomes (via improved adherence)
- Impact on overall cost of pharmaceuticals and medical spending
- Impact on competitive outlook for innovative new medicines
- Impact on efforts to design formularies based on cost-effectiveness of pharmaceuticals
- Feasibility of implementation
- Ability to improve transparency of costs to support public dialogue on value and affordability

5.2. OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)

Arrangements between PBMs and health plans which specify 100% pass-through of rebates are becoming more common; we have already described how PBMs are decreasingly dependent on rebates, passing more through to the payer. A more universal move to requiring 100% pass-through arrangements with alternative ways of paying for PBM services could be linked to a move to flat fees for distributors and pharmacies, helping to wean the entire drug delivery chain off of reliance on rebates and percentage fees. Although payers argue that flexibility in the amount of pass-through is helpful, given that plan sponsors have different priorities, many believe that the overall system is moving rapidly toward a near-universal 100% pass-through even without federal action of some kind.

Potential advantages

The most obvious and important potential advantage of this model is that it would eliminate any incentive for PBMs to favor higher list prices just to recoup greater revenue through higher rebates. Net prices could remain confidential, and rebates could, in principle, continue to be linked to utilization at the population level. Proponents also believe that passing all rebates – and any other form of manufacturer fee or payment – back to plan sponsors would allow payers to compare PBM offerings more transparently and improve the negotiating power of payers over the rewards of PBMs and others in the delivery chain. This alternative rebate model could also improve transparency for the individual payer so that they understand why certain decisions are being made by a PBM with regards to formulary design.

Another potentially beneficial effect of moving to a universal pass-through model is that PBMs might then need to compete more directly on patient management and the value for money of the drugs utilized. Without rebates, PBMs might put more emphasis on distinguishing themselves in the marketplace by achieving superior patient outcomes, for example through methods such as provider education and helping ensure patients receive and take their medications. It could also facilitate adoption of value-based formularies based on cost-effectiveness, although use of post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign.

The implementation of this model would involve relatively little disruption to the overall drug delivery system but would still entail a difficult transition from existing contracts without a 100% pass-through with the need to introduce new ones going forward that would require all rebates to be passed back to payers. It should be noted that this arrangement would impact different types of plans differently. It would not impact Medicare Part D for which 100% pass-through is already mandated through the return of all direct and indirect remuneration (payments or payment adjustments made after the point-of-sale) which must be paid back to CMS.

Potential disadvantages

This alternative model would achieve little for patients if the increased rebates flowing back to plan sponsors are not reflected in lower co-pays (i.e. if this reform were not implemented alongside requirements around applying rebates to the point of sale – see option 2). The potential impact on the gross-to-net gap and overall spending is also unclear because many plans now expect, and some may prefer, to have large and guaranteed rebates.

In addition, the primary potential advantage of a pass-through model may also represent one of its greatest potential disadvantages for both payers and patients. If PBMs are paid a fixed fee independent of negotiated rebates, they could have less incentive to put great effort into fighting for the lowest net price. However, PBMs say that in current 100% pass-through contracts their interests remain aligned with payers to achieve the lowest net prices possible.

Further, it is important to consider whether requiring PBMs to pass along all rebates to plan sponsors might limit PBMs efforts to benefit from economies of scale in negotiating lower prices. The PCMA's response to the HHS Blueprint highlighted this issue in relation to Medicare Part D, in particular asking whether imposing a requirement that PBMs act solely in the interest of the Part D plan sponsor might prohibit the practice of PBMs aggregating rebates across multiple plans. Under current practice, PBMs achieve savings through the use of economies of scale and purchasing power, negotiating with manufacturers across multiple Part D plans so as to achieve greater savings than a single plan could on its own. If PBMs are prohibited from aggregating rebates across multiple Part D plans, it might lead to a reduction in negotiating leverage, and therefore higher overall net costs for payers.

For health plans that contract for PBM services there are also implications of 100% pass-through on the calculation of the plans' Medical Loss Ratio (MLR). Money retained from rebates by PBMs is counted as a medical cost for the health plan, which may help them reach the legally required MLR. If PBMs shift all rebates to health plans and receive the same overall amount by being paid fees instead, this would count as an increase in administrative cost for the health plan and indirectly put pressure on their ability to meet the necessary MLR. This could require reductions in some plan premiums.

Finally, a 100% pass-through model would be viable for public payers but paying contracted PBMs fees for their efforts could raise problems in some states bound by cost-based regulatory guardrails that put restrictions on how a Medicaid program can pay an additional profit margin to a third party.

Discussion

Given that 100% pass-through is already in place for many PBMs and plans, this represents the least radical option. However, whilst it may seem a simple solution, to mandate 100% pass-through would require a reform to the contracting process. There are many who question whether this approach would really tackle the gross-to-net gap issue, as PBMs would still aim to achieve high rebates for their customers, who may still have limited awareness or understanding of formulary decisions made at the PBM level, and therefore focus on the size of rebate. Some contest that the issue is not ensuring 100% pass-through, but creating better transparency in contracts outlining what exactly is being passed-through and what is being retained by PBMs, with some suspicion that rebate dollars are being retained in the guise of administrative fees. Mandating 100% pass-through of rebates would require careful definition of what constitutes a full rebate dollar, and delineation of all the fees associated with rebates.

5.3. OPTION 2: Point of Sale (POS) rebates for patients

The impact of rising list prices on patient cost sharing has been one of the prime motivating forces behind the search for alternative rebate models. The vast majority of patients with both public and private insurance have their out of pocket payment for prescription drugs tied to the list price, not the net price after rebates. Systems are not set up to provide a POS rebate for individual patients for several reasons. First, since many rebates are tied to utilization at the group/population level and are determined post hoc, it is difficult to assign a precise rebate level for a drug at the POS. Second, some commentators have worried that POS rebates would include information for patients that inadvertently discloses the gross to net price gap, thereby eliminating confidentiality of the rebate level and undermining the negotiating power held by payers through their ability to get confidential rebates. Lastly, POS rebates by their very nature, give to individual patients some of the money that would otherwise flow back to the payer. The payer no longer has the option to apply those funds in ways that reduce overall health insurance premiums.

Despite these challenges, POS rebates are already offered by many PBMs and a few health plans as well, although most report limited uptake. According to a CVS report in August 2018, of the total rebates returned to CVS Health by CVS Caremark, \$6.3 million were used at the POS to lower out-of-pocket costs, which improved adherence by between 4 and 6%.²⁵ Whilst it appears that uptake of POS rebates by health plans has been low, this is increasingly being considered. In March 2018, UnitedHealthcare (UHC) announced that it would provide POS rebates to 7 million enrollees.⁵⁴ UHC has rolled out a POS plan option for its fully insured business, but not for Medicaid, Medicare, or individual plans. In order to prevent simple back-calculation of rebate amounts from individual patient payment details, the rebate passed through to the patient at the POS does not reflect 100% of the true rebate. Varying the amount of the POS rebate is also necessary to maintain good alignment of patient out-of-pocket requirements with the lowest cost alternatives in the formulary. Although this model lacks perfect transparency, it meets the goal of helping patients reap at least some of the benefit from negotiated rebates, and UHC believes this model is easier to administer while also preventing POS from undermining the plans' ability to negotiate the lowest net price possible without it becoming known to competitors.

It will be important to strike a balance between averaging all discounts (termed “peanut butter spreading”) which does not improve transparency, and total transparency for each drug, which will adversely impact the ability of plans and PBMs to negotiate lower net prices. Health plans and PBMs think that this is achievable. An illustration of the possible Impact of a POS Discount on Member Payments in the pharmacy is set out in Table 5.1 below.

We can see that the impact on patients varies, depending both on which plan design they have and on which phase of their deductible they are in. This makes estimating the impact on plan finances of the introduction of POS discounts difficult.

Table 5.2: Illustration of Possible Impact of a POS Discount on Member Payments

Prescription Cost (List Price)	Drug Cost Discount (Rebates)	
\$400	\$250	
Plan Phase of the Patient	Member pay <i>without</i> POS Discount	Member pay <i>with</i> POS Discount
Deductible	\$400	\$250
20% Coinsurance	\$80 (\$400*20%)	\$50 (\$250*20%)
\$35 Copay	\$35	\$35

Adapted with permission from an illustration by UnitedHealthcare

Potential advantages

Action taken to require POS rebates with any rebate at the payer level could have several important advantages. First, patients who require extended use of expensive medications for chronic conditions could have their financial burden lessened. For example, patients in high-deductible health plans who pay the list price each month for insulin (until their deductible is reached) may be paying hundreds—or even thousands—more annually than their insurer is paying for the drugs. By reducing financial toxicity, it is likely that adherence with prescriptions will improve, increasing patients’ health and potentially sparing downstream health costs attributable to ineffectively treated conditions. Whilst further evidence of this effect is required, there are numerous studies internationally that demonstrate the association between out-of-pocket patient costs and lower treatment adherence. An IHS Markit report specifically models the potential impact of POS rebates on spending by patients, medication adherence, and subsequent healthcare resource savings through reduced hospitalizations and diabetes-related complications.⁵⁵ The authors find that passing through 80% of rebates for diabetes medicines to the patient at the POS could generate 10-year medical savings of \$20 billion. Secondly, aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies if patient co-pays are lowest, as a consequence of the POS rebates, for the most cost-effective treatment.

Potential disadvantages

POS rebates by themselves are not a cure for the financial burdens faced by many patients who need high-cost medicines but only have access to health insurance benefit designs with high deductibles and/or co-insurance. POS rebates would also not neutralize the incentives for PBMs and others in the drug delivery chain that may lead them to seek higher list prices and larger rebates. They would not lower the aggregate cost of prescription drugs overall, nor help reduce health insurance premiums, which some stakeholders view as the priority for any change to the current rebate system. As noted earlier in the discussion of the UHC introduction of POS plans, another potential risk is that unless POS rebates are not carefully calibrated, they could reduce the out-of-pocket cost of a branded drug to the extent that these are chosen by members in place of generics that cost less to the plan.

Applying rebates at the point of sale will reduce out-of-pocket cost for specific individuals who are on high cost medications but would not impact the most economically vulnerable patients on Medicaid, whose copayments are kept low already. For these patients, as well as others who have reached their out-of-pocket maximums in their respective plans, the rebate savings will continue to flow directly to the payer.

Multiple potential disadvantages have been noted if POS rebates were implemented for patients in Medicare Part D. Some fear that POS rebates would unfairly benefit manufacturers, as reduced out-of-pocket costs would lead to fewer patients reaching the coverage gap phase (where manufacturers must provide a discount of 70%). It has been estimated that brand drug manufacturers would pay out nearly \$10 billion to \$29 billion *less* in price discounts in the Part D coverage gap over ten years because of fewer patients reaching the coverage gap.⁵³

Importantly, it is also possible that POS rebates would lead plans to increase premiums enough to have an important negative impact on the affordability of Medicare Part D plans for financially vulnerable patients. CSRxP noted that HHS actuaries have estimated that the policy could cost taxpayers between \$27 billion to \$82 billion over ten years, depending on the minimum rebate amount, as increasing premiums would require more federal subsidy for enrollees. But even with increasing subsidies, they and others believe that even small increases to Medicare Part D premiums may lead financially vulnerable elderly patients to forego signing up for Medicare Part D entirely. The Medicare Payment Advisory Commission (MedPAC) was one of several groups expressing this concern and, consequently, it “strongly encourage[d]” CMS to find a less complex policy to lower out-of-pocket spending for Part D enrollees.⁵⁴

Discussion

The debate around rebate reform has been driven by commentary on the affordability of drugs in the U.S. system, particularly for patients. Mandated POS rebates would most directly target this issue, and therefore may be the most politically viable or attractive option. However, some argue that POS rebates would simply shift costs around for patients and enrollees, who may perceive reduced cost-sharing at the expense of higher premiums to be unattractive; for those patients with chronic conditions who would still meet their deductible limits, there would be little gain. Whilst the evidence is limited, there is some indication that POS rebates could improve adherence and consequently clinical outcomes.

As well as the impact on patients, plans need to understand the impact of POS rebates on premiums. Plans are likely to favor strategic use of POS rebates at a plan level, which can be adapted based on employer or payer type; therefore, a law mandating 100% pass-through of rebates to the POS is unlikely to be well received. There are multiple ways in which POS rebates could be designed. Following the approach being used by UHC (and potentially others), a *proportion* of the rebate could be applied at the POS, and/or POS rebates might be only applied to certain specialty drugs for specific patient populations. These design elements are key. They also raise important questions about whether payers have the technology solutions needed to implement an effective POS system. Clearly, some major health plans and PBMs do have these capabilities, but it is unclear whether the entire health system has this capacity. To guide future private market offerings and federal policy making it would be helpful to gain a better understanding of how technology can facilitate various POS models. More information is also needed on how POS rebates impact patient spending and plan premiums, but this is likely to vary a great deal depending on benefit structure and specific patient characteristics.

5.4. OPTION 3: Eliminate rebates and move to upfront discounts

Some commentators believe that moving to upfront discounts is a viable alternative that would accomplish the chief aims of many stakeholders. Fein has set out the most detailed description of how a discount model could work, including suggestions for product movements, financial flows and contract relationships.⁵⁸ He sets out how this would address the current incentive problem, but also explores some of the implementation challenges, including (a) that this level of transparency could reduce the discounts manufacturers are willing to offer and (b) that it could cause conflict with outcome/value-based agreements.

Potential advantages

The main argument for upfront discounts in place of rebates is that it removes the PBM incentive to generate revenue from the gross to net gap that many feel can lead to higher list prices and a less transparent flow of money between manufacturers, PBMs, and payers. Upfront discounts could also be the alternative model that most facilitates the application of cost-effectiveness findings to the development of formularies. Since the effective price is known at the outset, cost-effectiveness can be determined and compared. Discounts could be allowed to vary depending on clear criteria such as cost-effectiveness or expected volume. Clinicians can more readily become involved in choosing the most cost-effective treatment for their patients. Rebate pass-through models would also help facilitate value-based formulary design but are more complicated because the final rebate level, and therefore net price, would not be known until some later time point (assuming it varies by utilization), and therefore the ultimate cost-effectiveness of any drug cannot be known at the time it is prescribed.

Potential disadvantages

None of the alternative rebate models has received as much criticism as has a shift to upfront discounts. Many have argued that upfront discounts would not provide the same level of negotiating power as rebates that can be linked to utilization/market share, leading to an increase in overall drug costs. The implicit transparency in upfront discounts is also viewed as problematic, potentially leading manufacturers to set single discount levels for all payers that would also increase costs. As mentioned previously, some have even argued that discounts would increase the risk of tacit collusion on price discounting among competing manufacturers.

In the legal settlement over 20 years ago that led to the abandonment of discounts in favor of rebates, drug manufacturers agreed they would not offer upfront volume discounts, and instead agreed to offer similar pricing contracts to all purchasers that demonstrated they could move market share. The legal context has not changed, so it is not clear whether manufacturers could legally offer upfront any differentiation of discounts without violating antitrust law. To facilitate the provision of fixed-priced discounts between manufacturers and payers/PBMs, Congress may need to undertake legislative action to amend the Sherman and Robinson-Patman Acts.

From a practical perspective, a move to a fixed-price discount approach is viewed by all stakeholders as requiring a major, complicated restructuring of both Medicare Part D and commercial contracts. Wholesalers and pharmacies could end up dealing with dozens of different (discounted) prices for each drug (varying by plan) and it is not clear how such a system would move such differently priced drugs through the supply chain.

Discussion

As described, a major argument against eliminating rebates is that negotiations could no longer be based on realized utilization/market share, meaning negotiating power for payers could be reduced. But this raises a key question: In today's market, are rebates usually linked with utilization? Multiple payers and manufacturers at the ICER Policy Summit said that the use of utilization-based rebates has nearly vanished from the marketplace, and even use of market-share based rebates has declined, as PBMs and payers have shifted to guaranteed rebate levels that provide greater certainty at an earlier time point that helps with overall budgeting. The PBMs and payers in turn seek guaranteed rebates from manufacturers. Hence the complexity of modelling that occurs by both parties as each seeks to calculate likely impact on their costs. If this is the case across the health system then a critical argument against the elimination of rebates disappears, and a move to upfront discounts in turn becomes more feasible.

What is indisputable is that eliminating rebates and moving to upfront discounts would have the potential to move the entire drug purchasing, negotiating, coverage, and delivery towards greater transparency and a firmer foundation on true value. The need to shield the exact amount of price discounts so that competing manufacturers would not be able to see each other's bids remains, however, a critical pre-condition for upfront discounts to be effective in driving down prices. And changing the system to eliminate rebates and implement upfront discounts would require the biggest change to the status quo; the implementation challenges are numerous, and therefore the legal and political barriers to this reform are likely to be high. And it is very important to consider the impact of moving away from rebates for Medicaid programs, which currently achieve notably higher rebate levels and are proportionately dependent upon them to meet budgets.

We might expect options that eliminate rebates entirely to reduce the level of resources currently being spent on the complex "rebate economy", where there are often multiple permutations of a rebate, with various complicated administration fees and price protections, leading to costly and labor-intensive calculations by all parties. In a system based on upfront discounts, plan sponsors and payers could shift their selection of PBMs away from looking predominately at rebate levels, and toward overall quality and value. However, both parties will still seek to calculate the impact of an upfront discount on their costs. It is still possible, however, that notwithstanding the initial implementation issues around a system of upfront discounts, once achieved it could offer a system that would be easiest and best for patients while also aligning the business models of the entire drug delivery chain in a beneficial manner.

5.5. A Summary of the Three Alternative Options against Relevant Criteria.

Our summary table is provided on the following page.

Table 5.3. Evaluating Alternative Rebate Models

	Option 1: 100% pass through of rebates to plan sponsors	Option 2: POS rebates for patients	Option 3: Eliminate rebates and move to upfront discounts
Impact on patients' affordability, access to care, and clinical outcomes (via improved adherence)	With less incentive for higher rebates, list prices and gross-net gap may decline, benefiting individual patients financially if their cost-sharing is linked to list price (which could lead to better adherence and outcomes).	Individual patients will see lower costs at the pharmacy counter, which could improve adherence and therefore clinical outcomes. However, the broader enrolled population may eventually face higher premiums.	Patients will have lower cost-sharing based on a discounted list price. Premiums may rise, however, if bargaining power is reduced.
Impact on overall cost of pharmaceuticals and medical spending	May increase rebates returned to plan sponsors but could also reduce incentive for PBMs to seek lowest net price if they are paid flat fees, so impact on overall cost of drugs uncertain. However, the change will impact the MLR which could require reductions in some plan premiums. Would not address the high computational effort and cost associated with the rebate economy.	Transparency of rebates at POS might decrease payer negotiating leverage (but depending on design, confidentiality could be maintained). Increase in plan drug costs because money returned to patients which could lead to premium increases. Overall health costs unlikely to change unless improved adherence drives down non-drug costs. Would not address the high computational effort and cost associated with the rebate economy.	Price concessions may not be as large since they are not linked to moving market share; however, if rebates are currently rarely linked with realized market share, then this disadvantage disappears. Upfront discounts could avoid the costly operational burden of rebate calculation. However, both parties will want to estimate the impact of an upfront discount on their costs.
Impact on competitive outlook for innovative new medicines	No improvement. If plan sponsors receive all rebates, they would have more incentive to favor existing drugs with substantial rebates over new entrant drugs with a single indication. PBMs could offer formularies favoring cost-effective new entrants and allow payers to choose lower list prices or higher list prices with larger rebates.	No direct effect.	New entrants could have improved competitive chances against existing drugs since discounts would not be linked to market share.
Impact on efforts to design formularies based on cost-effectiveness of pharmaceuticals	If 100% pass-through aligns PBM and plan sponsor incentives it could facilitate adoption of value-based formularies based on cost-effectiveness. But post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign at product launch. Requires plan sponsors to shift from focus on rebates to value-for-money.	Aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies.	Prices are known for formulary design, so provides the easiest platform to construct a value-based formulary based on cost-effectiveness.
Feasibility of implementation	Many PBMs are already offering pass-through options. Transition over time to mandatory model for all PBM-plan sponsor contracts not significantly disruptive.	Although some PBMs are already offering this option, implementation will involve changes in contractual arrangements and information flows.	Potential issues for reconciling the many differently negotiated discounted rates for thousands of drugs along the full supply chain. There is also legal uncertainty about the feasibility of this option.
Ability to improve transparency of costs to support public dialogue on value and affordability	Whilst transparency for payers could be improved if accompanied by clearer dialogue and understanding of rebates, public appreciation of value and affordability unlikely to be affected.	Allowing patients taking a drug to benefit directly from the rebates applied to it is likely to support public dialogue and understanding of value, but likely implementation routes are unlikely to achieve full transparency.	Transparency would be increased, which would support public dialogue on value and affordability. However, it would be possible to implement confidential discounts which would maintain payer bargaining power but not increase transparency of net prices.

6. Discussion

One solution does not fit all

Through our presentation of the three key options, and their assessment against several major considerations, it is apparent that there is no one ideal solution, and that their favorability turns on how one interprets the evidence as well as what can be hypothesized about future scenarios. On top of this, choosing the best policy option will rest on which goals are given the most weight. It is inevitable that stakeholders will vary according to what they most wish to see accomplished.

Whilst efforts to legislate the passing of rebates to payers and/or patients has appeal and is relatively less disruptive, this may not truly tackle the perverse incentive structure and system cost inherent to the rebate economy. Radical change involving the elimination of rebates in favor of upfront discounts has the potential to lead to a simpler system and could more easily facilitate value-based formulary based on cost-effectiveness, but the legal and political barriers to achieving this change are significant.

We have also assumed in our analysis that stakeholders are rational. To the extent that the proposed reforms *could* create a more rational incentive structure, and support a move to lowest net cost (though some contest this), they should be viewed as attractive policy options. However – though it defies logic – a real concern for some plan sponsors is that accounting models have been built around predictable, guaranteed rebates. Whilst this should not guide policy-makers, it may influence the attractiveness or otherwise of any reform in the short-term for some stakeholders.

Transparency versus simplicity and negotiating leverage

The degree of transparency – and the inherent trade-off with negotiating leverage – is rightly in the spotlight. Whilst confidentiality of the negotiated discount or rebate is more challenging to maintain for some options compared with others, for each policy option the level of confidentiality of discount represents a variable design option. There is likely to be a trade-off between transparency and simplicity in particular for options two and three. For POS rebates, decision-makers will need to decide the extent to which members should understand the amount they benefit from rebates, versus how much they want their members to get the most competitive rate based on a confidential negotiation. To maintain confidentiality and avoid back-calculations, patients would need to receive a variable percentage of the rebate at POS, perhaps linked to the average for the therapy class, which would not necessarily improve transparency as compared with the current situation, but should mean that patients pay less at the POS. The interaction between transparency and upfront discounts is also complex. Upfront discounts could be the model that most facilitates use of cost-effectiveness findings in the development of formularies. If the effective price is known at the outset, cost-effectiveness can be determined and compared. Clinicians can more readily become involved in choosing the most cost-effective treatment for their patients. However, it would be preferable for upfront discounts to be able to differ by product, which is likely to require the full level of those discounts to be confidential. The mechanism to achieve this is not clear given the ongoing use of high deductible plan designs in which patients themselves are responsible for the total cost up to a certain threshold. There may even be a trade-off. In the short run, requiring upfront discounts to be transparent may push up costs by reducing negotiating leverage and risking supplier collusion, but in the medium term it may facilitate the use of cost-effective drugs, increasing value for money.

Shortcomings of the proposed options

The overall implications for patient and health system costs for all the options discussed in this paper are not straightforward, and there are various aspects which are not well addressed by any of the proposed solutions. One such aspect is the impact of reform on the competitive outlook of innovative new medicines. In the current rebate system, manufacturers of new medicines with limited indications (and therefore market size) are constrained in the level of rebates they can offer, and therefore disadvantaged in formulary placement. This problem is not addressed by the options presented under rebate reform, but novel ways to address this and promote innovation could include:

- Rebates by indication: rebate volume positioning would only be permitted by indication, meaning that newer innovative drugs targeting a limited number of indications would not be disadvantaged.
- Rebates that do not convey preferred formulary access: decisions would be to include or exclude from the formulary, based on net cost. This would remove the existence of tiers, preferred status, stepped therapy etc., but may also reduce plan leverage to reduce costs.

There is also a completely different approach, which has not been presented explicitly in this paper: a system whereby cost-effectiveness criteria are used to establish a value-based price. With regards the three options presented, this fits most clearly with upfront discounts (the level of discount needs to be decided in some way, and this could be through a value-based assessment), but a more radical option would be to use cost-effectiveness to influence list price directly. To change to a value-based pricing system would represent a radical change to the U.S. system, but could address many of the issues being raised, and obviate concerns around the need to limit access for non-cost-effective drugs.

6.1. What else do we need to know?

There are various research questions that arise from our discussion of the various options. As well as understanding what the potential implications would be of a change to the rebate system, there are also several questions about today's arrangements which – if better understood – could help to offer clarity on the attractiveness of the alternatives. One such key question is:

- To what extent are rebates in the current system linked with utilization?

If they are not, then this eliminates one of the arguments against upfront discounts, which would not allow for discount to be linked with (realized) utilization. Other key questions arising are:

Reforming rebates:

- Would enforcing 100% pass-through of rebates to payers have a meaningful impact, given the trend toward this in today's market already?
- Would POS rebates involve a discount to patients that is significant enough to impact adherence?

- Data and evidence are required on the financial implications of POS rebates for plans; this may need to be mapped out on an individual patient basis, complicating planning efforts.

Replacing rebates:

- What would the Sherman Anti-trust Act mean today for a move away from rebates?
- Is there a way we could have upfront discounts that are known to the payer but not in the public domain?

In addition, for each option there needs to be careful consideration of the differential impact of reform for different payer types. For example, for POS rebates, would the impact on premiums be large enough to impact Medicare Part D coverage? If we eliminated rebates, what would be impact be for those that are most dependent on rebates in the current system (e.g. Medicaid)? How much of the Medicaid rebate is wrapped up in best price versus the inflation protection?

6.2. Conclusion

In this paper we have sought to bring clarity to the reason for the development of the current rebate system, and why it is has become so deeply entwined throughout the drug pricing, coverage, and delivery systems. As noted in the introduction, there are few who do not identify serious shortcomings of the current system. Among these, however, one stands out: that patients who require expensive medications are facing rapidly increasing financial burdens as list prices climb at high rates, even if increases in net prices after rebates are more modest. Rebates on a percent of list price skew the incentives of every single part of the drug delivery chain away from what is best for individual patients and for plan sponsors seeking the most cost-effective approach to providing good health coverage. And innovative life science companies can find that new drugs with superior effectiveness and lower prices still cannot get competitive traction when facing the scale of rebates that the makers of large market-share drugs have at their disposal.

And yet, rebates in their current form have played one essential role: they have given payers some element of negotiating leverage with manufacturers, especially in drug classes with multiple drugs of similar effectiveness. Forcing an abrupt transition away from rebates would raise significant questions about the impact on total costs of care and on patient access and outcomes. Even small effects that would increase health care insurance premiums might have significant effects on individuals who already struggle to afford health insurance for drugs through their employer, health insurance exchange, or Medicare. Any effort at reform should therefore realize the broad effects of any switch to an alternative rebate model. The potential for unintended consequences should be fully realized by policymakers.

Nearly all stakeholders in the health care system realize that some form of change in the traditional paradigm of rebates is needed, and the market has already led important shifts toward 100% rebate pass-through. Early efforts at establishing a POS rebate model to help patients reap the benefits of negotiated prices are also now in play, although it is too early to evaluate the outcomes. Nonetheless, an aspirational target of moving fully toward a system in which upfront discounts could be part of a broader transformation in drug negotiation and delivery is shared by a surprising number of stakeholders. A future health care system whose incentives are fully aligned toward rewarding value while improving access and outcomes for patients will require more radical change than simply giving patients part of the rebate at the POS. We hope this white paper will chasten policymakers who might have seen eliminating rebates or any of the other options as an easy, clean procedure. We equally hope that it will hearten and inform those who wish to take a thoughtful, careful approach to near-term reform while laying the groundwork for a greater transformation to come.

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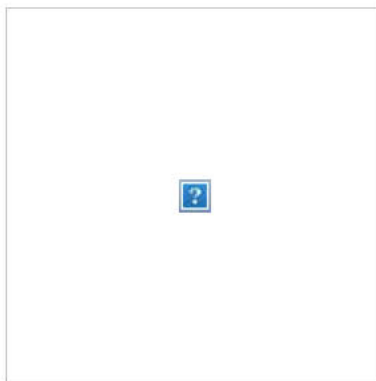
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Subject: ICER Weekly View: January 25, 2019
Date: Friday, January 25, 2019 8:05:13 AM



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[hikes](#) (FiercePharma)



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Baker backs rate-setting for high-cost drugs (CommonWealth Magazine)

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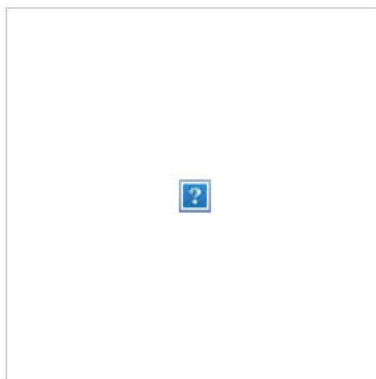
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Subject: ICER Weekly View: January 25, 2019
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From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Gov Baker's Proposal
Date: Monday, January 28, 2019 10:13:54 AM

Kaha,

I hope you are well. We were excited to see Governor Baker's proposal last week in his budget about prescription drugs at MassHealth. We'd love to understand the proposal more in detail, and understand what the process is going forward. Do you know who we should talk to?

As an aside, we would truly love your feedback on the final draft of the white paper I sent around late Friday. You brought really important perspective to our meeting, and we've made some fundamental shifts based on your comments (especially with regards to the outcomes-based contracting framing).

Celia Segel

Celia S. Segel, MPP
Director of CER Policy Development
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From: [Laura Cianciolo](#)
To: [Laura Cianciolo](#)
Cc: [Matt Seidner](#)
Subject: ICER: Logistics Update and Clinical Expert Call Details
Date: Thursday, January 31, 2019 2:44:47 PM
Attachments: [ICER SMA Meeting Agenda 030719.pdf](#)

Good Afternoon,

In preparation for our March 7 New England CEPAC Public Meeting on SMA, I wanted to send out an update that the meeting will now begin at 9:30 am (instead of 10:00 am) and run until 4:00 pm. Prior to the official start of the meeting, we'll have our usual pre-meeting discussion and breakfast from 8:15-9:15 am. Please see the attached agenda for an overview of the day.

We've also finalized the date and time for our clinical expert call (details below) and I'll send out a calendar appointment shortly. We will be joined by Dr. Emma Ciafaloni, a professor of neurology at the University of Rochester, and Dr. David Michelson, a pediatric neurologist at Loma Linda University Health. Both doctors also served on the American Academy of Neurology nusinersen guideline panel. Prior to this call, we kindly ask that you read at least the executive summary of the revised report, which will be released on February 21. As always, we'll provide a recording of the call after its conclusion for anyone who is unable to attend.

New England CEPAC SMA Clinical Expert Call

Thursday, February 28, 2019 11:00 AM - 12:00 PM EST

Dial-in: **Exemption N**

Access Code: **Exemption N**

If you would like to ask questions via the chat window, please join using this URL:

Exemption N. You may also ask questions verbally throughout the call.

Please feel free to reach out with any questions. We look forward to seeing you all in March!

All the best,
Laura

Laura Cianciolo
Program Associate
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Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Thursday • March 7, 2019 • 9:30 am to 4:00 pm

Alcott Ballroom, Omni Parker House, 60 School Street, Boston, MA 02108

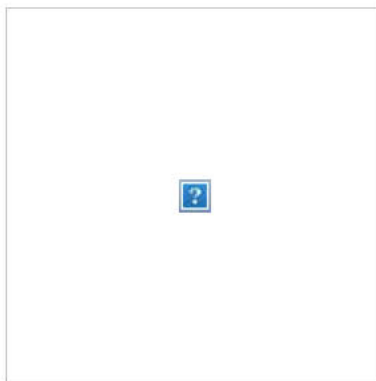
Time	Activity
9:00 am—9:30 am	Registration for Public Attendees
9:30 am—9:45 am	Meeting Convened and Opening Remarks Steve Pearson, MD, MSc, President, ICER
9:45 am—10:45 am	Presentation of the Evidence Alexandra Ellis, PhD, MSc, AM, Senior Scientist, ICER Matt Stevenson, PhD, BSc, Professor, University of Sheffield
10:45 am—11:00 am	Manufacturer Comments and Discussion
11:00 am—11:30 am	Public Comments and Discussion
11:30 am—12:30 pm	Lunch
12:30 pm—2:00 pm	New England CEPAC Vote on Clinical Effectiveness and Value
2:00 pm—2:15 pm	Break
2:15 pm—3:30 pm	Policy Roundtable
3:30 pm—4:00 pm	Reflections from New England CEPAC
4:00 pm	Meeting Adjourned

From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Weekly View: February 1, 2019
Date: Friday, February 01, 2019 7:02:54 AM



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[ICER Weekly View: February 1, 2019](#)

From the desk of David Whitrap

Good morning, everyone. I'm sure many of you are gearing up for an exciting Super Bowl, but I personally will have difficulty rooting for either 1) [the team that stole a championship from my hometown](#) or 2) [the team that abandoned my hometown altogether](#).

So instead, I plan on Sunday to focus my energy on snacks (other than sour grapes), commercials, and [the optimal betting strategy for "Super Bowl Squares."](#)

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[CVS to cover migraine drugs from Teva, Lilly; excludes Amgen \(Reuters\)](#)

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[Novartis Sees High Demand for Possible Multi-Million Dollar Drug](#)

(Bloomberg)

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Countering the promising developments in sickle-cell, this week brought us yet another disappointing setback in the search for treatments for Alzheimer's.

All Eyes on Biogen as Roche Alzheimer's Drug Flunks Final Test (Xconomy)

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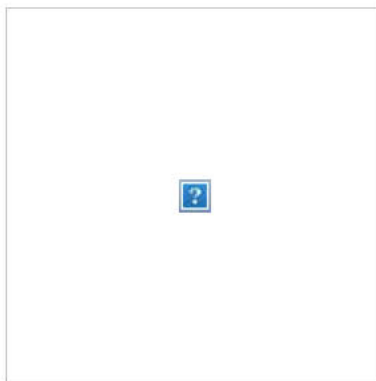
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From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Re: Gov Baker's Proposal
Date: Tuesday, February 05, 2019 8:05:45 AM

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Celia

Sent from my iPhone

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From: [Maggie O'Grady](#)
To: [NE CEPAC Council](#)
Cc: [Matt Seidner](#)
Subject: Save the Date: New England CEPAC July Retreat
Date: Wednesday, February 06, 2019 12:10:00 PM

Dear New England CEPAC Members,

I am writing to let you know that we have scheduled our annual New England CEPAC retreat for the evening of **July 24, 2019**. This is the day before the New England CEPAC Public Meeting on Therapies for Duchenne Muscular Dystrophy, which will take place in Cambridge, MA.

We would like to have all CEPAC members attend the retreat, so please plan your travel for the public meeting accordingly.

The retreat will take place from 5:30pm-9pm, and will include a brief reception, a group discussion reflecting on the last year and your suggestions for improvements for the coming year, and dinner. We will host the retreat at a restaurant close to the hotel. We have not yet selected a venue for the retreat, but will let you know as soon as we do.

Please note that this is a different format from past retreats, which have traditionally taken place over a half day. We are trying this new format to make the best use of Council members' time, but may return to the half-day format in the future.

Thank you again for your participation in the New England CEPAC, and please don't hesitate to reach out if you have any questions about the public meeting or retreat.

All the best,
Maggie

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From: [Celia Segel](#)
Subject: FW: Feedback on Final Draft of Rebates Paper
Date: Thursday, February 07, 2019 2:33:57 PM
Attachments: [Final Draft - ICER OHE White Paper on Rebates.pdf](#)
[ATT00001.htm](#)

Good afternoon!

This is just a reminder that we need all feedback on our final draft of the white paper by tomorrow end of day. We recognize that the Trump administration issued their proposed rule last week on rebates, and we will need to make some important contextual updates to the paper.

Thanks in advance for your thoughts!

Celia

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From: Celia Segel <csegel@icer-review.org>
Sent: Friday, January 25, 2019 3:01 PM
To: Steve Pearson <spearson@icer-review.org>
Subject: Feedback on Final Draft of Rebates Paper

Dear Members,

I am pleased to present our final draft of the post-Summit white paper on alternatives to rebates. We learned a huge amount from all of your expertise during the summit, so before we circulate this paper more broadly to the public, we hope you will provide us with one more round of commentary. Please note that this final draft should be kept internal to your organizations as it is not yet public.

Please send us your comments and edits on this final draft no later than February 8.

We have greatly enjoyed hearing your insights onto this very important and timely topic. We look forward to hearing your thoughts on this final paper.

Celia Segel

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VALUE, ACCESS, AND INCENTIVES FOR INNOVATION: POLICY PERSPECTIVES ON ALTERNATIVE MODELS FOR PHARMACEUTICAL REBATES

January 2019

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TABLE OF CONTENTS

Executive Summary.....	ES1
1. Introduction.....	1
1.1. Context.....	1
1.2. Our Approach.....	2
1.3. How do rebates work?	3
1.4. History of the Transition from Discounts to Rebates	4
1.5. Perspectives on the “Gross-to-Net” Price Gap	5
2. Rebates in Different Insurance Markets.....	7
2.1. Medicaid	9
2.2. Medicare	10
2.3. Commercial Markets.....	11
Flow of rebates from PBMs to payers	11
Flow of rebates from PBMs and payers to patients	12
3. How do rebates impact different stakeholders?	13
3.1. Empirical studies on the impact of rebates	13
3.2. Rebates and the Flow of Revenue Within the Pharmacy Supply and Financing System.....	14
3.3. Public Comments on Rebate System Alternatives from Different Stakeholders.....	15
4. Key aspects for consideration of reform	16
4.1. Transparency of Rebate Amounts	16
4.2. Maintaining the possibility of implementing outcome-based contracts.....	17
5. What are the alternative options for rebate models?	18
5.1. Major Considerations for Alternative Rebate Models.....	19
5.2. OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)	19
5.3. OPTION 2: Point of Sale (POS) rebates for patients.....	21
5.4. OPTION 3: Eliminate rebates and move to upfront discounts	24
5.5. A Summary of the Three Alternative Options against Relevant Criteria.	26
6. Discussion	28
7. References	32

Executive Summary

The combination of rising drug costs at the health system level and increasing financial stress for individual patients has triggered intense national concern. One target has come under particular scrutiny: rebates.

Drug makers and payers (including both insurers and pharmacy benefit managers [PBMs]) negotiate discounts to the list price of drugs (rendered post-sale as rebates) in exchange for preferential formulary placement which increases sales. Rebates are a key negotiating tool for payers, and help produce a lower “net” price for drugs that can help reduce the overall costs of drug spending. But for many years the PBM business model has included a revenue stream gained by retaining a small percent of the absolute rebate amount they return to plan sponsors. Drug makers argue that this “rebate economy” forces them to increase list prices in order to offer ever larger rebates to PBMs to gain preferred formulary status. The effect of rebates in lowering net prices may reduce plan sponsor costs and therefore help moderate the cost of insurance premiums for all plan members, but higher list prices hurt those patients who need ongoing drug treatment, since patients are required to pay their out-of-pocket share for drug coverage in relation to the list price, not the negotiated rebate price.

Rebates have therefore become an extremely contentious topic, praised by many as the best tool available to provide competitive leverage for payers seeking lower net prices, but reviled by others who view it as the chief sin in a system that punishes sick patients with higher out-of-pocket costs and absorbs billions of dollars that could otherwise either reward innovation or keep costs down, or both. Recently, both payers and drug makers have introduced new approaches that experiment with alternative approaches to rebates. Meanwhile, the Trump administration is exploring regulatory action that could lead to dramatic changes to rebates. But what is known about how the rebate system interacts with other elements of drug pricing, coverage and delivery? And, for different stakeholders, what are the potential benefits and possible negative consequences of realistic possible alternatives? This White Paper, benefitting from interviews with numerous participants in the rebate process – from plan sponsors, to insurers, to PBMs, to drug makers – addresses these questions and lays out a framework for evaluating proposed alternatives to a rebate model that has served as the cornerstone of drug pricing and coverage negotiation for decades.

What are the major alternative options for rebate models?

There are three major alternative options to the current rebate model. The first two options represent rebate “reform” and may be combined, but it is important for policy makers to consider the potential advantages and disadvantages of each element separately. The third option would involve eliminating rebates.

OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)

The first option is to require that PBMs pass 100% of rebates through to plan sponsors in order to eliminate the incentive for PBMs to develop formularies that drive utilization to highly rebated drugs despite higher net costs for payers. PBMs would be paid instead solely through fees from plan sponsors. Although arrangements between PBMs and health plans which specify 100% pass-through of rebates are already becoming more common, a more universal requirement could be linked to a move to flat fees for distributors and pharmacies, helping to wean the entire drug delivery chain off of reliance on rebates and percentage fees.

Potential advantages: With less incentive for PBMs to develop rebate-driven formularies, financial incentives for high list prices will diminish, benefiting individual patients financially if their cost-sharing is linked to list price (which could lead to better adherence and outcomes). Net prices could remain confidential, and rebates could, in principle, continue to be linked to formulary placement and utilization at the population level. Proponents also believe that passing all rebates – and any other form of manufacturer fee or payment – back to plan sponsors would allow payers to compare PBM offerings more transparently and improve the negotiating power of payers over the rewards of PBMs and others in the delivery chain. This alternative rebate model could also improve transparency for the individual payer so that they understand why certain decisions are being made by a PBM with regards to formulary design.

Another potentially beneficial effect of moving to a universal pass-through model is that PBMs might then need to compete more directly on patient management and the value for money of the drugs utilized. Without rebates, PBMs might put more emphasis on distinguishing themselves in the marketplace by achieving superior patient outcomes, for example through methods such as provider education and helping ensure patients receive and take their medications. It could also facilitate adoption of value-based formularies based on cost-effectiveness, although use of post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign.

The implementation of this model would involve relatively little disruption to the overall drug delivery system but would still entail a difficult transition from existing contracts without a 100% pass-through.

Potential disadvantages: This alternative model would achieve little for patients in the short term if the increased rebates flowing back to plan sponsors are not reflected in lower co-pays (i.e. if this reform were not implemented alongside requirements around applying rebates to the point of sale – see option 2). The potential impact on the gross-to-net gap and overall spending is also unclear because many plans now expect, and some may prefer, to have large and guaranteed rebates.

In addition, the primary potential advantage of a pass-through model may also represent one of its greatest potential disadvantages for both payers and patients. If PBMs are paid a fixed fee independent of negotiated rebates, they could have less incentive to put great effort into fighting for the lowest net price.

Further, it is important to consider whether requiring PBMs to pass along all rebates to plan sponsors might limit PBMs efforts to benefit from economies of scale to achieve greater savings beyond what a single plan could on its own. If PBMs are prohibited from aggregating rebates across multiple Part D plans, it might lead to a reduction in negotiating leverage, and therefore higher overall net costs for payers and plan members.

Finally, these reforms will not impact Medicare plans as the law already requires that payers who participate in Medicare Part D pass all negotiated discounts (direct and indirect remuneration [DIR]) back to the government.

OPTION 2: Point of Sale (POS) rebates for patients

POS rebates involves passing rebate savings directly to patients. This option appears to most directly address the problem of high out-of-pocket costs, and some plans already offer, or are experimenting with, POS rebates. However, systems are not generally set up to provide a POS rebate for individual patients, since many rebates are tied to utilization at the group/population level and are determined post hoc. Therefore, it is difficult to assign a precise rebate level for a drug at the POS.

Potential advantages: Action taken to require POS rebates with any rebate at the payer level could have several important advantages. First, patients who require extended use of expensive medications for chronic conditions could have their financial burden lessened. Whilst the evidence is limited, there is some indication that POS rebates could improve adherence and consequently clinical outcomes. Second, aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies if patient co-pays are lowest, as a consequence of the POS rebates, for the most cost-effective treatment.

Potential disadvantages: Some commentators worry that POS rebates would include information for patients that inadvertently discloses the gross to net price gap, thereby eliminating confidentiality of the rebate level and undermining the negotiating power held by payers through their ability to get confidential rebates. In addition, POS rebates by themselves are not a cure for the financial burdens faced by many patients who need high-cost medicines but only have access to health insurance benefit designs with high deductibles and/or co-insurance. POS rebates would also not neutralize the incentives for PBMs and others in the drug delivery chain that may lead them to seek higher list prices and larger rebates.

POS rebates give to individual patients some of the money that would otherwise flow back to the plan sponsor. The payer no longer has the option to apply those funds in ways that reduce overall health insurance premiums, which some stakeholders view as the priority for any change to the current rebate system. Another potential risk is that unless POS rebates are carefully calibrated, they could reduce the out-of-pocket cost of a branded drug to the extent that these are chosen by members in place of generics that cost less to the plan.

Applying rebates at the point of sale will reduce out-of-pocket cost for specific individuals who are on high cost medications but would not impact the most economically vulnerable patients on Medicaid, whose copayments are kept low already. For these patients, as well as others who have reached their out-of-pocket maximums in their respective plans, the rebate savings will continue to flow directly to the payer.

Multiple potential disadvantages have been noted if POS rebates were implemented for patients in Medicare Part D. Some fear that POS rebates would lead plans to increase premiums enough to have an important negative impact on the affordability of Medicare Part D plans for financially vulnerable patients.

OPTION 3: Eliminate rebates and move to upfront discounts

Although most stakeholders believe that eliminating rebates in favor of upfront discounts would prove the most disruptive possible alternative model to the current rebate system, some commentators believe that moving to upfront discounts is both feasible and the best way to accomplish the chief aims of many stakeholders.

Potential advantages: The main argument for upfront discounts in place of rebates is that it removes the PBM incentive to generate revenue from the gross to net gap that many feel can lead to higher list prices and a less transparent flow of money between manufacturers, PBMs, and payers. Upfront discounts could also be the alternative model that most facilitates the application of cost-effectiveness findings to the development of formularies. Since the effective price is known at the outset, cost-effectiveness can be determined and compared. Discounts could be allowed to vary depending on clear criteria such as cost-effectiveness or expected volume. Clinicians could more readily become involved in choosing the most cost-effective treatment for their patients.

Potential disadvantages: Many have argued that upfront discounts would not provide the same level of negotiating power as rebates that can be linked to utilization/market share. The implicit transparency in upfront discounts is also viewed as problematic, potentially leading manufacturers to set single discount levels for all payers that would also increase costs. Some have argued that publishing discounts would increase the risk of tacit collusion on price discounting among competing manufacturers.

In the legal settlement 22 years ago that led to the abandonment of discounts in favor of rebates, drug manufacturers agreed they would not offer upfront volume discounts, and instead agreed to offer similar pricing contracts to all purchasers that demonstrated they could move market share. The legal context has not changed, so it is not clear whether manufacturers could legally offer upfront any differentiation of discounts without violating antitrust law.

In addition, from a practical perspective, a move to a fixed-price discount approach is viewed by all stakeholders as requiring a major, complicated restructuring of both Medicare Part D and commercial contracts. Wholesalers and pharmacies could end up dealing with dozens of different (discounted) prices for each drug (varying by plan) and it is not clear how such a system would move such differently priced drugs through the supply chain. It also may have significant implications for “best price” rule payments by manufacturers to State Medicaid plans.

Discussion

There is no perfect solution that eliminates all the challenges created by rebates while leaving payers with a similar level of negotiating leverage to help moderate costs. Forcing an abrupt transition away from rebates would raise significant questions about the impact on total costs of care and on patient access and outcomes. Even small increases in health care insurance premiums might have significant effects on individuals who already struggle to afford health insurance for drugs through their employer, health insurance exchange, or Medicare. Any effort at rebate reform should therefore realize the broad effects and the potential for unintended consequences.

Nonetheless, nearly all stakeholders in the health care system realize that some form of change to the current paradigm of rebates is needed, and the market is already moving toward 100% rebate pass-through. Early efforts at establishing a POS rebate model to help patients reap the benefits of negotiated prices are also now in play, although it is too early to evaluate the outcomes. Nonetheless, an aspirational target of moving fully toward a system in which upfront discounts were part of a broader transformation in drug negotiation and delivery is shared by a surprising number of stakeholders. A future health care system whose incentives are fully aligned toward rewarding value while improving access and outcomes for patients will require more radical change than simply giving patients part of the rebate at the POS. We hope this white paper will chasten policymakers who might have seen eliminating rebates or any of the other options as an easy, clean procedure. We equally hope that it will hearten and inform those who wish to take a thoughtful, careful approach to near-term reform while laying the groundwork for a greater transformation to come.

1. Introduction

1.1. Context

As pharmaceutical spending has risen in the US, health plan sponsors, insurers, and Pharmacy Benefit Managers (PBMs) have faced increasing challenges to maintain affordability. Among the mechanisms that have been implemented to try to control overall costs, health insurance benefit designs based on high initial deductibles and co-insurance within a tiered drug formulary have been effective, but have placed ever greater financial burdens on patients, especially those who require expensive on-going treatment for chronic conditions. The combination of rising drug costs at the system level and increasing financial stress for individual patients has triggered intense national concern.^{1,2} Policy makers across the political spectrum are eager to find root causes, highlight unfair market practices, and find solutions that can control drug costs and improve patient access and affordability.

As policy solutions have been sought, one target has come under increasing scrutiny: rebates. Rebates are a staple of negotiations between pharmaceutical companies and payer organizations (which we define as including health insurers and PBMs) and represent a *quid pro quo*: discounts to the list price of drugs (rendered post-sale as rebates) are offered in exchange for preferential formulary placement. Concern about drug prices initially brought negative attention to the role played by drug makers in setting and raising prices, but soon the focus was expanded to include the role that “middlemen” such as PBMs played in rebate negotiations.^{3,4} The claim against PBMs is that a substantial part of their revenue has traditionally come from keeping a percent of the absolute rebate amount they can negotiate, thereby creating a pernicious incentive to favor higher list prices from which a larger rebate can be obtained. Although the net price to insurers and plan sponsors might not change if increases in list prices are matched by correspondingly larger rebates, patients face the full impact of higher list prices since it is to these prices that benefit designs link out-of-pocket requirements. Rebates have therefore rapidly become an extremely contentious topic, still praised by many as the best tool available to provide competitive leverage for payers seeking lower net prices, but reviled by others who view it as the chief sin in a system that punishes sick patients with higher out-of-pocket costs and absorbs billions of dollars that could otherwise either reward innovation or keep costs down, or both.⁵

Some stakeholders have also noted that rebates can warp the competitive landscape for new drugs trying to compete with existing drugs that have broader indications and significant market share, allowing their manufacturers to offer far more substantial rebates to PBMs and payers.⁶⁻⁸ For example, in crowded drug classes such as autoimmune therapies, some drug makers have contended that new drugs with only a single indication, including some biosimilars, cannot get preferable formulary placement over existing leading drugs, even when new drugs are shown to offer better outcomes at a lower price, because the older drugs have multiple indications and billions of dollars of sales, generating rebates that are so substantial that payers would lose money by switching to the more cost-effective options for a single indication.⁹

Given these concerns, calls for reform of the rebate system have multiplied. In 2018 the Trump administration made clear its own dissatisfaction with the current rebate system and sought public comments on options for alternative models.¹⁰ While still considering public comment, in July 2018, the Trump administration moved forward and submitted a proposed draft rule to the Office of Management and Budget (OMB) to scale back legal protections that allow rebates within federal insurance systems without triggering anti-kickback provisions.¹¹ The proposed rule, whose provisions remain unknown at this time while awaiting approval by the Office of Management and Budget, have raised speculation that major changes will be introduced in the allowed scope and nature of rebates.¹²

Private companies have also responded to the rapidly evolving policy debate targeting rebates. In September 2018, Gilead announced that it would launch authorized generics of its two best selling drugs for Hepatitis C – Epclusa® and Harvoni® – with steep discounts of 68% and 62% off of their list prices for a course of treatment.¹³ Payers will now be able to choose between the discounted authorized generic and the full-price rebated drug. In October 2018, Amgen announced they would lower the list price of their cholesterol drug, Repatha, by 60% in lieu of seeking a similar net price through steep rebates.¹⁴ To capitalize on these moves by drug makers, and to lay the groundwork for further private market action to reduce the role of rebates, Express Scripts announced that it would offer a new “Flex” formulary option in 2019 to allow plan sponsors to select options with lower list prices and no rebates over options of the same drugs paid at a higher list price and corresponding rebate. Express Scripts said its explicit goal was to offer formulary designs that can ‘reduce reliance on rebated brand products.’¹⁵

With action within the federal government and the private market, the US thus appears poised for dramatic changes to a fundamental part of the drug pricing and coverage landscape. But what is known about how the rebate system interacts with other elements of drug pricing, coverage and delivery? And, for different stakeholders, what are the potential benefits and possible negative consequences of realistic possible alternatives? This White Paper, benefitting from interviews with numerous participants in the rebate process – from plan sponsors, to insurers, to PBMs, to drug makers – seeks to address these questions and to lay out a framework for evaluating proposed alternatives to a rebate model that has served as the cornerstone of drug pricing and coverage negotiation for decades.

1.2. Our Approach

This White Paper is structured to provide first an overview of the development of the current rebate system (section 1); describe how rebates flow between manufacturers, payers, and patients (section 2); explore what impact rebates have on key stakeholders in the health care system (section 3); outline two key aspects for consideration of reform (section 4); and analyze the potential consequences of alternatives that might replace the current rebate model (section 5). We conclude in section 6 with an analysis of key policy perspectives to guide future consideration of alternative rebate models, before offering a final discussion of the issues in section 7.

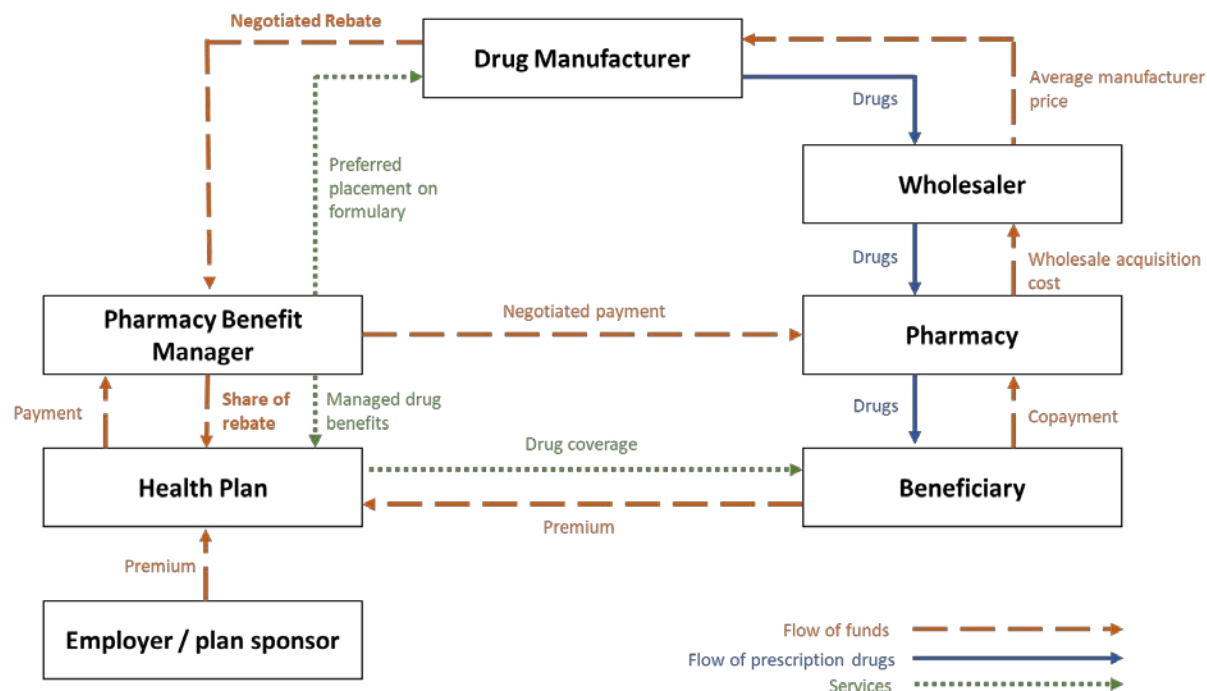
In preparing the paper we undertook a focused literature review and evaluated the written responses to the HHS Blueprint on drug pricing from key stakeholders, including all participants in the ICER membership program. We also conducted ten interviews covering PBMs, public and private payers, manufacturers, academics, benefit consultants, and trade associations. An earlier version of this paper was sent out as a pre-read for the ICER members Policy Summit. This version of the paper takes account of the discussion at that meeting.

Throughout this paper we describe how all alternatives to the current rebate system offer potential risks or disadvantages as well as potential benefits, and that the implementation of any major reform may pose daunting practical challenges given the multitude of ways that rebates affect various parties within the drug delivery chain. We outline the evidence presented to date, and the key questions that still need to be answered. Like an operation deep inside the brain, extracting the current rebate system and implanting something new would require careful attention to intricate structures, a steady hand, and very precise interventions in order for the patient to ultimately emerge safe and improved.

1.3. How do rebates work?

The supply chain for pharmaceuticals in the U.S. is complex, involving many different stakeholders with competing interests. Sood et al.¹⁶ calculate that 41% of prescription drug expenditure accrues toward intermediaries in the pharmaceutical distribution system. The following figure illustrates the flow of services, products, and payments (including rebates).

Figure 1.1. Simplified illustration of the flow of products, payments and services in the pharmaceutical supply chain



Source: Illustration based on Congressional Budget Office¹⁷

Rebates are negotiated between drug makers and payers (insurers or PBMs) when drugs first enter the market and can be renegotiated on a regular or ad hoc basis. As mentioned earlier, rebates are used as an element of negotiating favorable placement within a drug formulary. For example, a company desiring its drug to be placed in a best tier of formulary, in which the drug can be considered a “preferred” drug for clinicians, with more limited drug management and low out-of-pocket payments required from patients, may offer a larger rebate off the announced list price.

Rebates are thus more common and usually larger in drug areas in which there is significant competition, especially when competition is among drugs with similar mechanisms of action and only incremental, if any, differences in clinical risks or benefits. Drug areas with substantial rebates include drugs for diabetes and autoimmune agents used for conditions such as rheumatoid arthritis and psoriasis.

Although rebate levels are negotiated “upfront” before the drugs are prescribed, they are not implemented as discounts on the initial price paid, either by the payer or by the patient. Instead, rebates are paid retroactively, and may include a sliding scale based on the volume of prescriptions or market share. In other words. The rebate will be greater, i.e. a lower net cost, if the number of prescriptions is higher, reflecting a trade-off between net price and volume. Where relevant, PBMs share all or some portion of rebates with the health insurer or the plan sponsor based on their contractual agreement.

Manufacturers say that they can offer larger rebates if they increase their list prices. However, as discussed in Section 1.5, the relationship between list price trends and trends in rebates is not straightforward.

1.4. History of the Transition from Discounts to Rebates

Historically, PBMs competed by negotiating terms with pharmacy networks, managing the delivery of specialized pharmaceutical products, and processing prescription transactions (claims) on behalf of health plans. The role of PBMs has expanded from claims processing, to the development of formulary management, which has coincided with their exercising of market power to negotiate with drug manufacturers to encourage competition on prices in drug categories where there are multi-source products or several on-patent products competing in a therapeutic area.

Prior to 1996, manufacturers offered discounts to health plans for their drugs, while charging an undiscounted list price to wholesalers and pharmacies. Wholesalers would then bill the manufacturer for the difference between the amount they purchased the drug for from the drug manufacturer, and the amount they were reimbursed by the pharmacy as determined by the health plan. Pharmacies, however, had no direct relationship with the drug manufacturer and could not reconcile their payment; so, while they paid full retail price for the drug to the wholesaler (plus a wholesaler markup), they were only reimbursed for the amount as determined by the health plan based on a negotiated rate with the drug manufacturer. Despite attempts by pharmacies to cut out wholesalers and collectively bargain with drug manufacturers to obtain more competitive rates, none were offered.

In 1996, a class action lawsuit was brought by retail pharmacies against major drug manufacturers alleging that they had violated the Sherman Antitrust Act and were hampering competition by negotiating upfront price discounts only with payers, and not with independent and chain pharmacies.¹⁸ The outcome of this lawsuit saw manufacturers enter into a court-approved settlement in which they agreed that they would (1) not refuse to discount goods based solely on the status of the buyer entity and (2) offer the same types of discounts previously reserved for plans to pharmacies and retail buying groups that could demonstrate an ability to affect market share in the same manner.¹⁸ As a result, manufacturers restructured their contracts with payers based on retroactive rebates tied to prescription volume and market share rather than upfront discounts. Pharmacies would be paid by payers for the drug at the price at which it was obtained from the wholesaler plus any supply chain markups. And payers would then receive any retroactive rebate direct from the drug manufacturer.

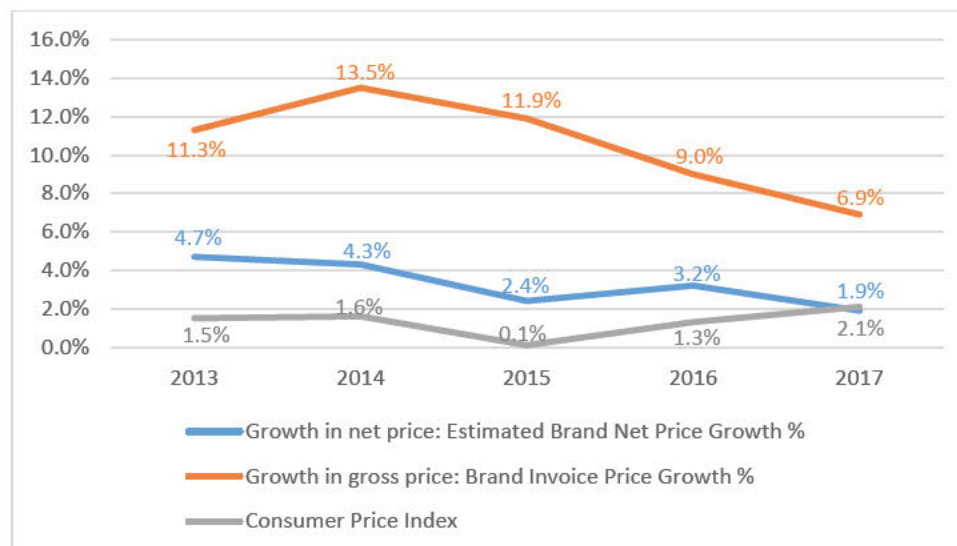
In reaction to this evolving landscape toward rebates and away from upfront discounts, the Office of the inspector General at HHS issued a “safe harbor” protection in the late 1990s to shield drug companies’ rebate contracts from the implications of the Anti-Kickback Statute (AKS). The AKS prohibits remuneration for referrals or services that are payable by a federal program (i.e. Medicare) - in effect paying someone to recommend your product under a federal health care program.¹⁹ In place since 1971, this safe harbor provision is now being questioned by HHS. Its revocation by the federal government could serve as a powerful tool to reshape the discount/rebate structure in federal health programs with knock-on implications for private sector health insurance markets.

1.5. Perspectives on the “Gross-to-Net” Price Gap

Opinions on the magnitude of the difference between list prices and net prices following rebates, and the role that rebates play in driving overall drug expenditures, are highly contentious across different stakeholders and commentators. Manufacturers say that they can offer larger rebates if they increase their list prices, which is supported by some analyses linking increased overall spending on rebates with increasing list price trends.²⁰ However, studies commissioned by the Pharmaceutical Care Management Association (PCMA) and the America’s Health Insurance Plans (AHIP) demonstrate no positive relationship between list price levels and the amount obtained in rebates for specific drugs and drug classes.^{20,21}

There is general agreement that the gap between list price and net price is widening as a cumulative sum: over the five years between 2012 and 2016 the total value of pharmaceutical manufacturers’ off-invoice rebates and other price concessions more than doubled from \$59 billion to \$127 billion.^{22,23} IQVIA has shown that invoice price growth (i.e. gross price) has continually out-paced net price growth (which accounts for rebates), and both have been above inflation (with the exception of net price growth in 2017); this is shown in Figure 1.2.

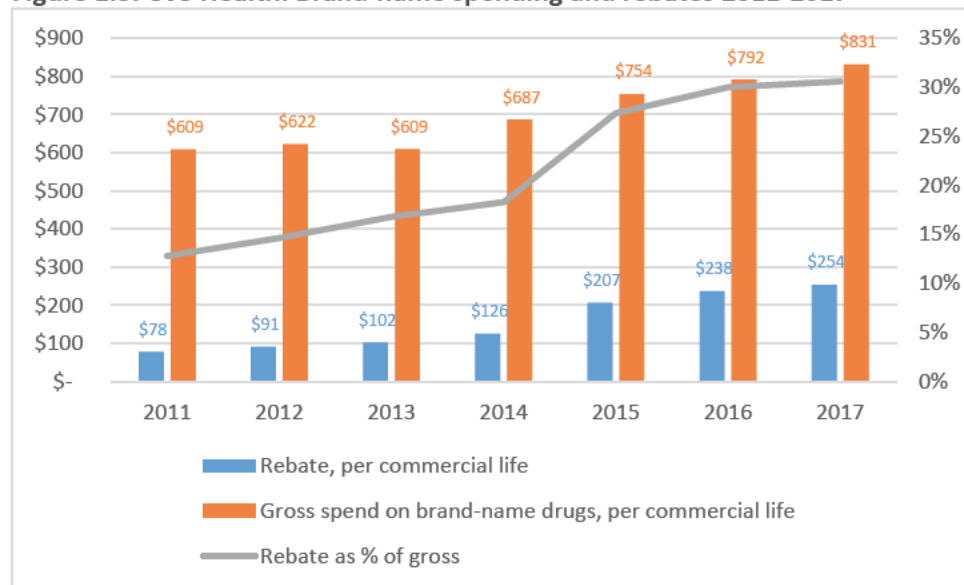
Figure 1.2. IQVIA data on protected^a brands gross and net price growth 2013-2017



Source: Data from IQVIA²²

Data from the Office of the Inspector General (OIG) and CVS corroborate this growing gap between list price and net price.^{24,25} In a 2018 report, OIG demonstrates that while reimbursement for Medicare Part D increased 62% from 2011 to 2015 (\$49 billion to \$80 billion), rebates more than doubled (\$9 billion to \$23 billion) over the same timeframe.²⁴ CVS data also demonstrate that whilst gross expenditure on brand-name drugs has increased, the corresponding level of rebate has increased faster, leading to a higher proportion of gross expenditures being rebated from 13% in 2011 to 31% in 2017; this is represented in Figure 1.3.

Figure 1.3. CVS Health: Brand-name spending and rebates 2011-2017



Source: Data from CVS Health²⁵

For patients, the gap between list and net price can substantially affect out-of-pocket spending at the pharmacy counter. In the past decade, employers and individuals have shifted toward benefit designs with high out-of-pocket cost structures, including deductibles, co-insurance, and tiered formulary design. Patients' out-of-pocket expenditure has been linked to list prices instead of net prices since net prices are considered proprietary and are only determined retroactively. A large gap between list and net price therefore matters to patients, who, in some cases, might pay more out-of-pocket for the drug than its actual true (net) cost to the plan.²⁶ Examples of patients paying high out-of-pocket costs, without benefiting from the rebates negotiated for a therapy, have become commonplace in mainstream news throughout the past several years, including high profile stories about insulin and the EpiPen.^{27,28}

^a Protected brands are products that have been on the market two years or more and have yet to reach patent expiry.

2. Rebates in Different Insurance Markets

The size of rebates on branded drugs vary across public and private insurance carriers. Werble et al. estimated that negotiated rebates are, on average, approximately 30% of the list (WAC) price.²⁹ Roehrig found that Medicare Part D plans achieve higher average rebates (31%) than private plans (16%),²⁸ and Medicaid, where state governments have the additional leverage of the “best price” rule, receives the highest average rebates on branded drugs (61%). Rebates also differ by drug types; a study of Medicare Part D rebates found that rebates were highest for drugs with brand competition (average 39% of gross cost), while protected class drugs^b had lower average rebates: 14%.³⁰

A 2016 study commissioned by the PCMA estimated that “from 2016 to 2025 the current use of PBM tools in the market place will save plan sponsors and consumers approximately \$654 billion.” The authors break this down by plan type: \$350 billion for commercial plan sponsors and their members, \$257 billion for Medicare Part D, and \$48 billion for Medicaid.³¹ In Table 2.1, below, we summarize the main characteristics of the different types of plan and how rebates work within each.

^b There are six protected classes (anticonvulsants, antidepressants, antineoplastics (including many oral chemotherapy drugs), antipsychotics, antiretrovirals, and immunosuppressants. Part D plans to cover “all or substantially all drugs” within each of the classes.

Table 2.1. How rebates work in different insurance schemes

	Medicaid	Medicare Part D	Medicare Part B	Private insurance (for comparison purposes)
Total drug expenditures ^{a,b}	\$62 billion	\$142 billion	\$26 billion	\$194 billion
Estimated rebate achieved off list price for brand name drugs ^c	61%	31%	No incentive to provide rebates and no estimate identified in the literature.	16%
Who are rebates negotiated by?	Innovators must provide a rebate of 23.1% of AMP ^d , or the manufacturer's "best price", whichever is greater. Supplemental rebates are negotiated by State Agencies (or PBMS on their behalf)	Commercial Plans (who often use PBMs)	Medicare pays providers ASP ^e + 6%	Commercial Plans (who often use PBMs)
How do rebate negotiations impact access for patients?	Status on Preferred Drug List	Drug management (Tiers, Prior Authorization, Exclusions) and cost sharing	Not applicable	Drug management (Tiers, Prior Authorization, Exclusions) and cost sharing
Where do savings from rebates go?	Medicaid / state	Reduced premiums (and therefore reduced government subsidies). Possible % retention by PBMs depending on arrangement, but all payment adjustments after the point-of-sale (including rebates) must be reported and given back 100% to CMS ^c .	Medicare	Reduced premiums and in some cases, reduced patient out-of-pocket costs. Possible % retention by PBMs depending on arrangement

^a Source: Roehrig³² for Medicaid, Medicare Part D and Private insurance. Reference year 2016, and represents total spend at the point of purchase, i.e. *prior to rebates* (\$).

^b Source: MedPAC³³ for Medicare Part B. Reference year 2015, and represents total spend on drugs and biologics based on average sales price (*accounts for rebates*)+6%

^c Source: Roehrig.³² Note these represent rebates achieved for brand name drugs. Estimated rebate for total point of sale drug spend (i.e. including generics) was 51%, 22% and 12% respectively.

^dAverage Manufacturer Price (AMP): Average price paid by wholesalers to manufacturers for drugs sold to retail pharmacy.

^eAverage Sales Price (ASP): Average price realized by a manufacturer to all purchasers, net of rebates, discounts and price concessions. Note: does not account for all rebates under the Medicaid program. Source: MedPAC.³³

2.1. Medicaid

Because of the Medicaid Best Price rule, introduced in the Omnibus Budget Reconciliation Act of 1990, Medicaid programs across the country obtain either (a) a minimum rebate of 23.1% off the average manufacturer price (AMP) for branded drugs or (b) the “best price” offered to any other public or private purchaser (whichever is the higher discount). The intent of this rule is to enable the public sector to get the benefits of private sector bargaining power and ensure the Medicaid program is not paying more than the private sector for its drugs.³⁴ In turn, Medicaid programs must cover all prescription drugs (with some exceptions).

State based Medicaid programs can negotiate deeper, “supplemental” rebates themselves or through a PBM. These negotiations are on a state-by-state basis, or sometimes achieved through cooperatives of states collectively bargaining on drug prices. State negotiated supplemental rebates can be applied to drugs purchased by all Medicaid managed care organizations contracted through the state. The impact of rebates on out-of-pocket costs for patients is not an issue in Medicaid, as beneficiaries have very low cost-sharing, which is often fixed and not related to drug cost. However, in order to incentivize negotiations for supplemental rebates, states can put therapies on a preferred drug list to streamline access for their members without drug management requirements.

Depending on the state Medicaid program, an important feature may be that rebates can be used to cross-subsidize other state spending. Given that Medicaid programs obtain substantial rebates, some PBMs believe that this revenue stream is so important to states that it reduces their interest in eliminating rebates.

There are several factors that contribute to the high rebate rates that are achieved under the Medicaid program. One is that manufacturers who refuse to participate in Medicaid are excluded by law from Medicare (which represents a much larger market share for prescription drugs). In addition, the government requires that Medicaid receive a minimum of 13% of AMP rebate on generic drugs.³² Between 2006 and 2009, the Office of the Inspector General (OIG) found that Medicaid recouped through rebates between 29% and 38% of its prescription drug expenditures each year, resulting in an average annual savings of about \$8 billion. These arise both from the best price rule and an additional rebate based on an inflationary component if the increase in a drug’s AMP exceeds the increase in the Consumer Price Index.

Private payers argue that the Best Price Rule sets an artificial floor for their negotiations, limiting their ability to negotiate rebates deeper than 23%. Soon after the creation of the Medicaid Drug Rebate Program (along with its ‘best price’ principle), payers viewed increased prices in the commercial sector as an effort by manufacturers to offset losses in the Medicaid program or to avoid “resetting” their best price. Both Congress and HHS have tried to address this effect by excluding certain prices, discounts, and rebates from the definition of AMP and best price.³⁵

^c There is a “risk corridor” within which plans can keep some additional revenues from rebates.

2.2. Medicare

There is no rebate program for Medicare Part B drugs. Rather, providers are paid the average sales price (ASP) plus 6%. The ASP is net of all rebates and price concessions, and therefore the program benefits indirectly from the rebates achieved by the rest of the market. In 2013 the OIG was asked to calculate the potential savings for Medicare if a rebate program similar to that of Medicaid (basic rebates and inflation-indexed rebates) were applied to Medicare Part B drugs; they estimated that savings of around 20% or more (\$2.7 to \$3.1 billion) could be realized, but that there were several implementation issues related to claims and data that would need to be addressed.³⁶ After receiving a Congressional request, the OIG conducted another analysis in 2017 that estimated savings of \$1.4 to \$1.8 billion could be realized for Part B drugs if inflation-indexed rebates accorded Medicaid were extended to Part B.³⁷

Under Medicare Part D, private insurers negotiate rebates with manufacturers independently with no government involvement, but all savings must be reported and paid to the government.^d As demonstrated in Table 2.1, Medicare Part D drugs obtain high rebates compared with those covered by private insurance. This is believed due to “the wider use of utilization management and multi-tiered and exclusionary formularies in Medicare Part D than in commercial plans [which] creates a greater risk/reward for the exclusion or inclusion of a manufacturer’s brand and encourages greater concessions through competitive forces.”³⁸ In addition, Medicare Part D beneficiaries are more sensitive to premium levels since many are on fixed incomes, and are therefore more likely to accept a restrictive formulary, enhancing the bargaining power of Part D plans.³²

While higher rebates in Part D compared to the commercial market may help moderate premium growth, cost-sharing for Part D patients is linked, as it is for commercially insured patients, to the list price. However, Medicare Part D has reinsurance for high cost patients who have over \$8,500 in estimated out-of-pocket drug costs. After this “catastrophic” threshold is met, the government picks up 80% of the bill, Part D plan liability is just 15%, with the remaining 5% paid by patients.^{39,40} A number of commentators have highlighted that this shift in financial responsibility at the catastrophic threshold gives PBMs and Part D plans an incentive to favor high-cost high-rebate drugs as high list prices push beneficiaries into the catastrophic phase more quickly, as the compulsory discount manufacturers are required to give patients is included in the patient cost calculation when determining whether the \$8500 threshold is reached.

The end effect has been that the share of the overall cost that Part D plans pay is decreasing as high-price, high-rebate arrangements increase. According to Antos and Capretta,³⁹ the government spent \$37 billion in 2017 covering expenses for beneficiaries above the catastrophic threshold, which was \$9 billion (about 25%) higher than in 2008. In line with this cost growth, the Medicare reinsurance subsidy (on a per member-per year basis) grew at an annual rate of nearly 17% between 2010 and 2015.⁴⁰ CMS policy makers have concluded that “Under current rules, Part D sponsors may have weak incentives, and, in some cases even, no incentive, to lower prices at the point of sale or to choose lower net cost alternatives to high cost-highly rebated drugs when available.”⁴¹

^d As noted in the footnote to Table 2.1 there is an exception for the risk corridor.

2.3. Commercial Markets

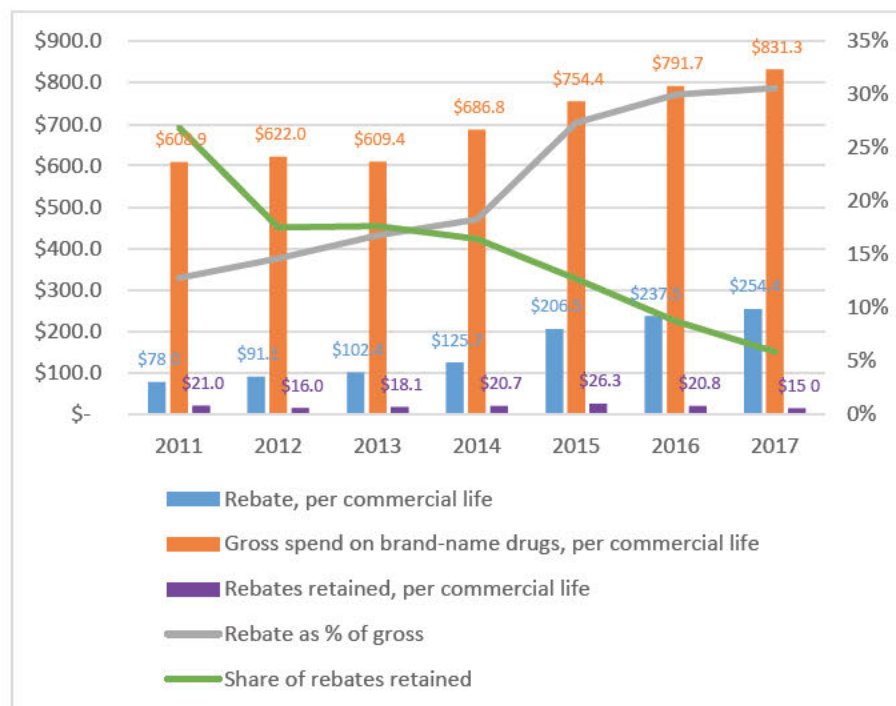
Flow of rebates from PBMs to payers

The contractual relationships between PBMs and payers take many different forms. As part of these contracts, PBMs often retain a percentage of rebates, although a growing number of payers are now seeking contracts in which all rebates are returned to the payer, often called a rebate “pass-through.”⁴² In some cases, PBMs offer a contract with a guaranteed level of rebate to the payer, an arrangement which subjects the PBM to more risk but offers the payer a predictable cash flow.²⁵

The percent and absolute amount of rebates retained by PBMs has been evaluated by different groups. A survey report from the Pharmacy Benefit Management Institute (PBMI) reported that just under half of employer respondents said they received 100% of rebates (either with a minimum rebate guarantee [27%] or without [22%]), a significantly higher percentage than similar estimates from 2014.⁴³ A recent study by Visante on behalf of PCMA states that, on average, around 90% of rebates are passed through to payers.²¹ Cumulatively, Roehrig finds that in 2016, \$89 billion in rebates were paid to health insurers, reducing total retail drug spending by 21%.³² This same study estimates total PBM profits to be \$11 billion and suggests that the notion that PBMs divert a large share of rebates to excess profits is not supported by the data.

Statements by two large PBMs – CVS and Express Scripts – also suggest that rebate retention is no longer a significant part of their business model. Data that CVS has published shows a downward trend in rebate retention over time.²⁵ Figure 2.1 illustrates the amounts in rebates obtained and retained by CVS from 2011 to 2017.

Figure 2.1. CVS Health: Brand-name spending, rebates and rebate retention 2011-2017



Source: Data from CVS Health²⁵

It can be observed from the Figure above that whilst rebates over time have increased substantially (from 13% of gross spend in 2011 to 31% in 2017), the share of those rebates retained by CVS has declined, from 27% in 2011 to just 6% in 2017. According to CVS, in the first half of 2018 CVS Caremark retained just 2% of rebates.²⁵ Similarly, Express Scripts states that they pass on 95% of rebates, and that nearly half of their clients opt for 100% pass-through of rebates.⁴⁴ The implication is that PBMs are shifting to charge for more of their services in other ways than taking a share of rebates.

Flow of rebates from PBMs and payers to patients

A 2017 PBMI report asked plan sponsors how rebates are used: 68% indicated that rebates are used to reduce plan spend on drug costs, whereas only 4% of plan sponsors were using rebates to reduce member out-of-pocket costs at the point of sale (POS). PhRMA and others critical of the lack of a POS rebate system for patients refer to this as “reverse insurance” in which those who need medications are required to pay more than others.^{45,8} It should be noted that some insurers, including major national carriers UnitedHealth Group and Aetna, have recently announced the introduction of POS rebate benefit designs.^{46,50}

3. How do rebates impact different stakeholders?

3.1. Empirical studies on the impact of rebates

There are a small number of empirical studies that consider the relationship between list price and rebate levels. They are as follows:

- A report by Milliman prepared for America's Health Insurance Plans (AHIP). This provides an analysis of historical Medicare Part D drug prices and manufacturer rebates. The report finds that brand drugs with rebates have higher historical list price trends than brand drugs without rebates.²⁰ However, among drugs with rebates, there is no difference in historical list price trends between drugs with higher rebates and those with lower rebates. In addition, the highest cost branded drugs have, on average, the lowest manufacturer rebates. The analysis does not analyze or hypothesize any causation for these relationships. What seems clear from the data is the impact of competition on rebates. More competition leads to higher rebates. However, this is not necessarily the same as lower net prices.
- CVS Health offers a response to what it describes as the "myth" about a positive relationship between rebate size and list price.²⁵ Its report, published in August 2018, argues that if this were the case, there would be a strong correlation between rebates and list prices. On the contrary, the report compares list price increases (2015 to 2018) with average rebates for six specific drug categories, showing that list price increases are higher for drugs with smaller rebates. According to the analysis, list prices for anticonvulsants and multiple sclerosis drugs rose over the time period by 46% and 27% respectively, while annual rebates were only 6% and 7%.^{25,47} However, the authors do not explain how the six drug categories were selected. Finally, they do not explore how list price increases might relate to changes to rebates over time. These explanations are important to differentiate between (1) therapy areas with only one or two manufacturers, where we might expect to see high prices, high price increases, and low rebates; and (2) competitive areas where we might see high list prices, high price increases, and high discounts.
- A report by Visante on behalf of PCMA similarly argues that there is no correlation between rebate levels and price increases by manufacturers.²¹ The authors' analysis suggests that among the top 200 brand drugs, there is no correlation between average rebate levels negotiated with PBMs and increasing prices set by manufacturers. Furthermore, they suggest that manufacturers raise prices even when rebates are low. This is consistent with the hypothesis that there are two different types of market: those where manufacturers have strong market power and those where there is a lot of competition.

- A 2016 Bloomberg analysis illustrates examples of the increasing divergence between list and net prices at the product level.⁴⁸ In a study of 39 products with global sales above \$1 billion per year, looking at the six-year period Q4 2009 to Q4 2015, they found that net prices after rebates increased at nearly the same rate as CPI inflation for 12 products (31%); for the other 27 products (69%), net prices rose well above inflation. For 31 of the products (79%), the percentage gap between list price and net price rose over the period. For the remaining eight (21%) it fell.

3.2. Rebates and the Flow of Revenue Within the Pharmacy Supply and Financing System

Given the number of parties involved in the pharmaceutical distribution and financing chain, and the confidential nature of the contractual arrangements between them, the flow of money is difficult to track. Two reports attempt to do so. Sood et al.¹⁶ look at the gross and net profit data of large publicly traded companies in this distribution chain. Their analysis demonstrates that for every \$100 spent in retail pharmacies, around \$17 compensates direct production costs, \$41 accrues to the manufacturer (\$15 of which is net profit), and the same amount (\$41) accrues to intermediaries: wholesalers, pharmacies, PBMs and insurers (with \$8 of net profit split among them). A study performed by the Berkley Research Group, sponsored by PhRMA, found that brand manufacturers captured 39% of initial gross drug expenditures; and 42% is captured by non-manufacturer entities.⁴⁹ In their analysis, wholesalers and pharmacies realized 22% of total drug spending; and payers and PBMs realized 20% of total drug spending.

3.3. Public Comments on Rebate System Alternatives from Different Stakeholders

The viewpoints of various stakeholders on the relative benefits and negative consequences of the current rebate system are understandably different. We reviewed the public comments submitted to HHS in response to its request for input. Table 3.1 summarizes the views of organizations participating in the ICER membership program, along with statements from major trade associations who responded directly to the HHS Blueprint. Our summary of the viewpoints is supplemented by information gained from telephone interviews undertaken with representatives of the key stakeholders.

Table 3.1. ICER Membership summary of comments to the HHS Blueprint

21/29 ICER Members submitted comments to HHS blueprint;
Also included are comments submitted by PhRMA, BIO, PCMA, and the Campaign for Affordable Rx Pricing Payers (<i>Anthem, HCSC, Aetna, AHIP, Cambia Health Services, United, Kaiser</i>) were most likely to:
○ Oppose prohibiting rebates (86%);
○ Support reforming Medicaid best price rule because of its impact on negotiating rebates (86%);
○ Oppose requiring point of sale rebates (86%).
PBM (CVS, Express Scripts, and PCMA) were most likely to:
○ Oppose prohibiting rebates (100%);
○ Oppose fixed price discounts (100%);
○ Support reforming Medicaid best price rule because of its impact on negotiating rebates (66%);
○ Support confidentiality (66%).
Pharmaceutical Companies (<i>Biogen, NPC, Genentech, GSK, Mallinckrodt, Merck Inc, Novartis, Regeneron, Sanofi, Alnylam, Astra Zeneca, Johnson and Johnson, PhRMA, BIO</i>) were most likely to:
○ Support Point of Sale rebates (71% Agree);
○ Were split on prohibiting rebates (36% yes; 21% no; 7% on the fence; 36% did not state);
○ Support confidentiality (14%).

4. Key aspects for consideration of reform

Before outlining the major policy alternatives to the current rebate system, in this section we highlight two important characteristics that should be carefully considered in weighing the pros and cons of any potential future model. These are: 1) transparency; and 2) the ability to administer outcome-based contracts. We introduce these topics in this section and elaborate where relevant within the discussion of the specific policy options in the next section. Both themes also appear in the major “criteria” that we propose for assessing policy options.

4.1. Transparency of Rebate Amounts

The desirability of transparency is contested by many stakeholders, both in responses to the HHS Blueprint and in other statements. Transparency of rebate amounts at the individual drug level is viewed by many as a direct outcome of eliminating rebates and moving to an upfront discount model. With other approaches in which rebates are retained in some fashion, transparency is more often viewed as optional, something that can be accommodated or that can be avoided.

Full price transparency throughout the drug delivery chain is seen by some as the only way for plan sponsors and insurers to fully understand the outcomes of their contractual relationship with PBMs and to ensure that rebates are flowing back to payers as intended. Similarly, it is argued that transparency of rebates and all other fees from manufacturers would limit the incentives of PBMs to include certain drugs in the formulary that generate more revenue for the PBM but which are not the most cost-effective for the payer. Transparency of rebates for the patient at the point of sale is held out as one way to increase pressure on payers and PBMs to share those rebates with patients.

In contrast, many others have argued that too much transparency could lead to higher net prices for two reasons. The first is that it could degrade the ability of manufacturers to offer larger rebates to certain payers. If all payers and PBMs know what the “best” rebate is in the marketplace, all would be able to seek it. As a response, manufacturers would be likely to calculate the most profitable *uniform* level of discount across all payers, which might result in higher net prices overall.

Second, some commentators worry that transparency could even lead to tacit collusion by competing manufacturers. The PCMA highlights in its response to the HHS Blueprint that the Federal Trade Commission (FTC) itself has stated that, “[i]f pharmaceutical manufacturers learn the exact amount of rebates offered by their competitors ... then tacit collusion among manufacturers is more feasible ... Whenever competitors know the actual prices charged by other firms, tacit collusion — and thus higher prices — may be more likely.”⁵⁰ CVS supports this point of view, reiterating that the Congressional Budget Office (CBO), FTC, and CMS have all expressed concerns regarding the competitive effects of disclosing drug-specific rebate data. The CBO has stated that the disclosure of rebates could impact Medicare spending for a number of medical conditions where there are only a few drugs available and thus the “disclosure of drug-by-drug rebate data in those cases would facilitate tacit collusion among those manufacturers, which would tend to raise drug prices.”⁵¹

4.2. Maintaining the possibility of implementing outcome-based contracts

Outcomes-based contracts, sometimes called “value-based contracts,” have become more common over the past decade. These contracts between drug manufacturers and payers feature increased rebates to payers if pre-specified clinical or economic outcomes are not achieved with treatment. For example, Harvard Pilgrim Health Care has announced outcomes-based based contracts with Amgen in which increased rebates for Amgen’s PCSK9 cholesterol drug are paid back to the insurer when the protective effect of the drug fails to prevent a heart attack or stroke.⁵² Whilst some commentators argue that the evidence is not convincing that outcomes-based contracts make an impact on cost or quality of care,⁵³ manufacturers, payers and policymakers (including the Trump administration) have identified outcomes-based contracts as one important mechanism for linking the overall payment for drugs to the value of the clinical outcomes they achieve.

It is important to note that outcome-based contracting cannot be viewed as a “solution” to the problems arising from rebates. It is likely to be limited to a very small number of drugs, and links to outcomes alone do not address concerns about highly price drugs at market entry. But given the general desire to facilitate further experimentation with outcomes-based contracts, consideration should be given to designing options to the current rebate model that will protect and, if possible, promote these efforts. They offer payers a mechanism to address uncertainty and to share risk that is inherent to the transition of drugs from a controlled clinical trial setting to the real-world.

5. What are the alternative options for rebate models?

Many different alternatives have been put forward by critics of the current rebate system. The major options, however, can be separated into two categories: 1) those that retain retroactive rebates but have some requirements to channel rebates back to payers and patients in prescribed ways; and 2) an alternative model that eliminates retroactive rebates entirely, replacing the current structure with upfront discounts. For shorthand, the first set of alternatives can be labeled as ways to “reform rebates” while the second moves formally to a system that “replaces rebates.” The two options to reform rebates could be implemented as stand-alone options or combined. In addition, all of the alternative rebate models can be implemented with varying degrees of transparency regarding the rebate/discount amount, but upfront discounts would most likely force transparency at the individual drug level, given that any linkage of patient payment to the discounted price would allow other stakeholders to gain knowledge of the discount.

The alternative options are portrayed below in Figure 5.1 and consist of:

- **Option 1:** Retain rebates with a requirement that PBMs pass on 100% of manufacturer rebates and fees to the plan sponsor.
- **Option 2:** Retain rebates with a requirement for point-of-sale (POS) rebates to patients.
- **Option 3:** Eliminate rebates in favor of a return to upfront discounts.

Table 5.1. Alternatives to the current rebate system

Reform Rebates	Replace Rebates
<ol style="list-style-type: none">1. 100% pass-through of rebates2. Point of Sale (POS) rebates applied to patient out-of-pocket cost sharing	<ol style="list-style-type: none">1. Eliminate rebates and move to upfront discounts

In the sections below, we describe each of these alternative options in greater detail. We also analyze their respective advantages and disadvantages, including practical considerations in their implementation. As noted earlier, both rebate reform options could be linked or could be implemented separately so we address them separately in the section below.

We begin by setting out possible criteria by which the different options could be judged and then, after discussing the options, we summarize the advantages and disadvantages in a Table.

5.1. Major Considerations for Alternative Rebate Models

We have focused on the following criteria by which the various alternatives can be evaluated:

- Impact on patients' affordability, access to care, and clinical outcomes (via improved adherence)
- Impact on overall cost of pharmaceuticals and medical spending
- Impact on competitive outlook for innovative new medicines
- Impact on efforts to design formularies based on cost-effectiveness of pharmaceuticals
- Feasibility of implementation
- Ability to improve transparency of costs to support public dialogue on value and affordability

5.2. OPTION 1: 100% Pass-through (All rebates flow to plan sponsors)

Arrangements between PBMs and health plans which specify 100% pass-through of rebates are becoming more common; we have already described how PBMs are decreasingly dependent on rebates, passing more through to the payer. A more universal move to requiring 100% pass-through arrangements with alternative ways of paying for PBM services could be linked to a move to flat fees for distributors and pharmacies, helping to wean the entire drug delivery chain off of reliance on rebates and percentage fees. Although payers argue that flexibility in the amount of pass-through is helpful, given that plan sponsors have different priorities, many believe that the overall system is moving rapidly toward a near-universal 100% pass-through even without federal action of some kind.

Potential advantages

The most obvious and important potential advantage of this model is that it would eliminate any incentive for PBMs to favor higher list prices just to recoup greater revenue through higher rebates. Net prices could remain confidential, and rebates could, in principle, continue to be linked to utilization at the population level. Proponents also believe that passing all rebates – and any other form of manufacturer fee or payment – back to plan sponsors would allow payers to compare PBM offerings more transparently and improve the negotiating power of payers over the rewards of PBMs and others in the delivery chain. This alternative rebate model could also improve transparency for the individual payer so that they understand why certain decisions are being made by a PBM with regards to formulary design.

Another potentially beneficial effect of moving to a universal pass-through model is that PBMs might then need to compete more directly on patient management and the value for money of the drugs utilized. Without rebates, PBMs might put more emphasis on distinguishing themselves in the marketplace by achieving superior patient outcomes, for example through methods such as provider education and helping ensure patients receive and take their medications. It could also facilitate adoption of value-based formularies based on cost-effectiveness, although use of post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign.

The implementation of this model would involve relatively little disruption to the overall drug delivery system but would still entail a difficult transition from existing contracts without a 100% pass-through with the need to introduce new ones going forward that would require all rebates to be passed back to payers. It should be noted that this arrangement would impact different types of plans differently. It would not impact Medicare Part D for which 100% pass-through is already mandated through the return of all direct and indirect remuneration (payments or payment adjustments made after the point-of-sale) which must be paid back to CMS.

Potential disadvantages

This alternative model would achieve little for patients if the increased rebates flowing back to plan sponsors are not reflected in lower co-pays (i.e. if this reform were not implemented alongside requirements around applying rebates to the point of sale – see option 2). The potential impact on the gross-to-net gap and overall spending is also unclear because many plans now expect, and some may prefer, to have large and guaranteed rebates.

In addition, the primary potential advantage of a pass-through model may also represent one of its greatest potential disadvantages for both payers and patients. If PBMs are paid a fixed fee independent of negotiated rebates, they could have less incentive to put great effort into fighting for the lowest net price. However, PBMs say that in current 100% pass-through contracts their interests remain aligned with payers to achieve the lowest net prices possible.

Further, it is important to consider whether requiring PBMs to pass along all rebates to plan sponsors might limit PBMs efforts to benefit from economies of scale in negotiating lower prices. The PCMA's response to the HHS Blueprint highlighted this issue in relation to Medicare Part D, in particular asking whether imposing a requirement that PBMs act solely in the interest of the Part D plan sponsor might prohibit the practice of PBMs aggregating rebates across multiple plans. Under current practice, PBMs achieve savings through the use of economies of scale and purchasing power, negotiating with manufacturers across multiple Part D plans so as to achieve greater savings than a single plan could on its own. If PBMs are prohibited from aggregating rebates across multiple Part D plans, it might lead to a reduction in negotiating leverage, and therefore higher overall net costs for payers.

For health plans that contract for PBM services there are also implications of 100% pass-through on the calculation of the plans' Medical Loss Ratio (MLR). Money retained from rebates by PBMs is counted as a medical cost for the health plan, which may help them reach the legally required MLR. If PBMs shift all rebates to health plans and receive the same overall amount by being paid fees instead, this would count as an increase in administrative cost for the health plan and indirectly put pressure on their ability to meet the necessary MLR. This could require reductions in some plan premiums.

Finally, a 100% pass-through model would be viable for public payers but paying contracted PBMs fees for their efforts could raise problems in some states bound by cost-based regulatory guardrails that put restrictions on how a Medicaid program can pay an additional profit margin to a third party.

Discussion

Given that 100% pass-through is already in place for many PBMs and plans, this represents the least radical option. However, whilst it may seem a simple solution, to mandate 100% pass-through would require a reform to the contracting process. There are many who question whether this approach would really tackle the gross-to-net gap issue, as PBMs would still aim to achieve high rebates for their customers, who may still have limited awareness or understanding of formulary decisions made at the PBM level, and therefore focus on the size of rebate. Some contest that the issue is not ensuring 100% pass-through, but creating better transparency in contracts outlining what exactly is being passed-through and what is being retained by PBMs, with some suspicion that rebate dollars are being retained in the guise of administrative fees. Mandating 100% pass-through of rebates would require careful definition of what constitutes a full rebate dollar, and delineation of all the fees associated with rebates.

5.3. OPTION 2: Point of Sale (POS) rebates for patients

The impact of rising list prices on patient cost sharing has been one of the prime motivating forces behind the search for alternative rebate models. The vast majority of patients with both public and private insurance have their out of pocket payment for prescription drugs tied to the list price, not the net price after rebates. Systems are not set up to provide a POS rebate for individual patients for several reasons. First, since many rebates are tied to utilization at the group/population level and are determined post hoc, it is difficult to assign a precise rebate level for a drug at the POS. Second, some commentators have worried that POS rebates would include information for patients that inadvertently discloses the gross to net price gap, thereby eliminating confidentiality of the rebate level and undermining the negotiating power held by payers through their ability to get confidential rebates. Lastly, POS rebates by their very nature, give to individual patients some of the money that would otherwise flow back to the payer. The payer no longer has the option to apply those funds in ways that reduce overall health insurance premiums.

Despite these challenges, POS rebates are already offered by many PBMs and a few health plans as well, although most report limited uptake. According to a CVS report in August 2018, of the total rebates returned to CVS Health by CVS Caremark, \$6.3 million were used at the POS to lower out-of-pocket costs, which improved adherence by between 4 and 6%.²⁵ Whilst it appears that uptake of POS rebates by health plans has been low, this is increasingly being considered. In March 2018, UnitedHealthcare (UHC) announced that it would provide POS rebates to 7 million enrollees.⁵⁴ UHC has rolled out a POS plan option for its fully insured business, but not for Medicaid, Medicare, or individual plans. In order to prevent simple back-calculation of rebate amounts from individual patient payment details, the rebate passed through to the patient at the POS does not reflect 100% of the true rebate. Varying the amount of the POS rebate is also necessary to maintain good alignment of patient out-of-pocket requirements with the lowest cost alternatives in the formulary. Although this model lacks perfect transparency, it meets the goal of helping patients reap at least some of the benefit from negotiated rebates, and UHC believes this model is easier to administer while also preventing POS from undermining the plans' ability to negotiate the lowest net price possible without it becoming known to competitors.

It will be important to strike a balance between averaging all discounts (termed “peanut butter spreading”) which does not improve transparency, and total transparency for each drug, which will adversely impact the ability of plans and PBMs to negotiate lower net prices. Health plans and PBMs think that this is achievable. An illustration of the possible Impact of a POS Discount on Member Payments in the pharmacy is set out in Table 5.1 below.

We can see that the impact on patients varies, depending both on which plan design they have and on which phase of their deductible they are in. This makes estimating the impact on plan finances of the introduction of POS discounts difficult.

Table 5.2: Illustration of Possible Impact of a POS Discount on Member Payments

Prescription Cost (List Price)	Drug Cost Discount (Rebates)	
\$400	\$250	
Plan Phase of the Patient	Member pay <i>without</i> POS Discount	Member pay <i>with</i> POS Discount
Deductible	\$400	\$250
20% Coinsurance	\$80 (\$400*20%)	\$50 (\$250*20%)
\$35 Copay	\$35	\$35

Adapted with permission from an illustration by UnitedHealthcare

Potential advantages

Action taken to require POS rebates with any rebate at the payer level could have several important advantages. First, patients who require extended use of expensive medications for chronic conditions could have their financial burden lessened. For example, patients in high-deductible health plans who pay the list price each month for insulin (until their deductible is reached) may be paying hundreds—or even thousands—more annually than their insurer is paying for the drugs. By reducing financial toxicity, it is likely that adherence with prescriptions will improve, increasing patients’ health and potentially sparing downstream health costs attributable to ineffectively treated conditions. Whilst further evidence of this effect is required, there are numerous studies internationally that demonstrate the association between out-of-pocket patient costs and lower treatment adherence. An IHS Markit report specifically models the potential impact of POS rebates on spending by patients, medication adherence, and subsequent healthcare resource savings through reduced hospitalizations and diabetes-related complications.⁵⁵ The authors find that passing through 80% of rebates for diabetes medicines to the patient at the POS could generate 10-year medical savings of \$20 billion. Secondly, aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies if patient co-pays are lowest, as a consequence of the POS rebates, for the most cost-effective treatment.

Potential disadvantages

POS rebates by themselves are not a cure for the financial burdens faced by many patients who need high-cost medicines but only have access to health insurance benefit designs with high deductibles and/or co-insurance. POS rebates would also not neutralize the incentives for PBMs and others in the drug delivery chain that may lead them to seek higher list prices and larger rebates. They would not lower the aggregate cost of prescription drugs overall, nor help reduce health insurance premiums, which some stakeholders view as the priority for any change to the current rebate system. As noted earlier in the discussion of the UHC introduction of POS plans, another potential risk is that unless POS rebates are not carefully calibrated, they could reduce the out-of-pocket cost of a branded drug to the extent that these are chosen by members in place of generics that cost less to the plan.

Applying rebates at the point of sale will reduce out-of-pocket cost for specific individuals who are on high cost medications but would not impact the most economically vulnerable patients on Medicaid, whose copayments are kept low already. For these patients, as well as others who have reached their out-of-pocket maximums in their respective plans, the rebate savings will continue to flow directly to the payer.

Multiple potential disadvantages have been noted if POS rebates were implemented for patients in Medicare Part D. Some fear that POS rebates would unfairly benefit manufacturers, as reduced out-of-pocket costs would lead to fewer patients reaching the coverage gap phase (where manufacturers must provide a discount of 70%). It has been estimated that brand drug manufacturers would pay out nearly \$10 billion to \$29 billion *less* in price discounts in the Part D coverage gap over ten years because of fewer patients reaching the coverage gap.⁵³

Importantly, it is also possible that POS rebates would lead plans to increase premiums enough to have an important negative impact on the affordability of Medicare Part D plans for financially vulnerable patients. CSRxP noted that HHS actuaries have estimated that the policy could cost taxpayers between \$27 billion to \$82 billion over ten years, depending on the minimum rebate amount, as increasing premiums would require more federal subsidy for enrollees. But even with increasing subsidies, they and others believe that even small increases to Medicare Part D premiums may lead financially vulnerable elderly patients to forego signing up for Medicare Part D entirely. The Medicare Payment Advisory Commission (MedPAC) was one of several groups expressing this concern and, consequently, it “strongly encourage[d]” CMS to find a less complex policy to lower out-of-pocket spending for Part D enrollees.⁵⁴

Discussion

The debate around rebate reform has been driven by commentary on the affordability of drugs in the U.S. system, particularly for patients. Mandated POS rebates would most directly target this issue, and therefore may be the most politically viable or attractive option. However, some argue that POS rebates would simply shift costs around for patients and enrollees, who may perceive reduced cost-sharing at the expense of higher premiums to be unattractive; for those patients with chronic conditions who would still meet their deductible limits, there would be little gain. Whilst the evidence is limited, there is some indication that POS rebates could improve adherence and consequently clinical outcomes.

As well as the impact on patients, plans need to understand the impact of POS rebates on premiums. Plans are likely to favor strategic use of POS rebates at a plan level, which can be adapted based on employer or payer type; therefore, a law mandating 100% pass-through of rebates to the POS is unlikely to be well received. There are multiple ways in which POS rebates could be designed. Following the approach being used by UHC (and potentially others), a *proportion* of the rebate could be applied at the POS, and/or POS rebates might be only applied to certain specialty drugs for specific patient populations. These design elements are key. They also raise important questions about whether payers have the technology solutions needed to implement an effective POS system. Clearly, some major health plans and PBMs do have these capabilities, but it is unclear whether the entire health system has this capacity. To guide future private market offerings and federal policy making it would be helpful to gain a better understanding of how technology can facilitate various POS models. More information is also needed on how POS rebates impact patient spending and plan premiums, but this is likely to vary a great deal depending on benefit structure and specific patient characteristics.

5.4. OPTION 3: Eliminate rebates and move to upfront discounts

Some commentators believe that moving to upfront discounts is a viable alternative that would accomplish the chief aims of many stakeholders. Fein has set out the most detailed description of how a discount model could work, including suggestions for product movements, financial flows and contract relationships.⁵⁸ He sets out how this would address the current incentive problem, but also explores some of the implementation challenges, including (a) that this level of transparency could reduce the discounts manufacturers are willing to offer and (b) that it could cause conflict with outcome/value-based agreements.

Potential advantages

The main argument for upfront discounts in place of rebates is that it removes the PBM incentive to generate revenue from the gross to net gap that many feel can lead to higher list prices and a less transparent flow of money between manufacturers, PBMs, and payers. Upfront discounts could also be the alternative model that most facilitates the application of cost-effectiveness findings to the development of formularies. Since the effective price is known at the outset, cost-effectiveness can be determined and compared. Discounts could be allowed to vary depending on clear criteria such as cost-effectiveness or expected volume. Clinicians can more readily become involved in choosing the most cost-effective treatment for their patients. Rebate pass-through models would also help facilitate value-based formulary design but are more complicated because the final rebate level, and therefore net price, would not be known until some later time point (assuming it varies by utilization), and therefore the ultimate cost-effectiveness of any drug cannot be known at the time it is prescribed.

Potential disadvantages

None of the alternative rebate models has received as much criticism as has a shift to upfront discounts. Many have argued that upfront discounts would not provide the same level of negotiating power as rebates that can be linked to utilization/market share, leading to an increase in overall drug costs. The implicit transparency in upfront discounts is also viewed as problematic, potentially leading manufacturers to set single discount levels for all payers that would also increase costs. As mentioned previously, some have even argued that discounts would increase the risk of tacit collusion on price discounting among competing manufacturers.

In the legal settlement over 20 years ago that led to the abandonment of discounts in favor of rebates, drug manufacturers agreed they would not offer upfront volume discounts, and instead agreed to offer similar pricing contracts to all purchasers that demonstrated they could move market share. The legal context has not changed, so it is not clear whether manufacturers could legally offer upfront any differentiation of discounts without violating antitrust law. To facilitate the provision of fixed-priced discounts between manufacturers and payers/PBMs, Congress may need to undertake legislative action to amend the Sherman and Robinson-Patman Acts.

From a practical perspective, a move to a fixed-price discount approach is viewed by all stakeholders as requiring a major, complicated restructuring of both Medicare Part D and commercial contracts. Wholesalers and pharmacies could end up dealing with dozens of different (discounted) prices for each drug (varying by plan) and it is not clear how such a system would move such differently priced drugs through the supply chain.

Discussion

As described, a major argument against eliminating rebates is that negotiations could no longer be based on realized utilization/market share, meaning negotiating power for payers could be reduced. But this raises a key question: In today's market, are rebates usually linked with utilization? Multiple payers and manufacturers at the ICER Policy Summit said that the use of utilization-based rebates has nearly vanished from the marketplace, and even use of market-share based rebates has declined, as PBMs and payers have shifted to guaranteed rebate levels that provide greater certainty at an earlier time point that helps with overall budgeting. The PBMs and payers in turn seek guaranteed rebates from manufacturers. Hence the complexity of modelling that occurs by both parties as each seeks to calculate likely impact on their costs. If this is the case across the health system then a critical argument against the elimination of rebates disappears, and a move to upfront discounts in turn becomes more feasible.

What is indisputable is that eliminating rebates and moving to upfront discounts would have the potential to move the entire drug purchasing, negotiating, coverage, and delivery towards greater transparency and a firmer foundation on true value. The need to shield the exact amount of price discounts so that competing manufacturers would not be able to see each other's bids remains, however, a critical pre-condition for upfront discounts to be effective in driving down prices. And changing the system to eliminate rebates and implement upfront discounts would require the biggest change to the status quo; the implementation challenges are numerous, and therefore the legal and political barriers to this reform are likely to be high. And it is very important to consider the impact of moving away from rebates for Medicaid programs, which currently achieve notably higher rebate levels and are proportionately dependent upon them to meet budgets.

We might expect options that eliminate rebates entirely to reduce the level of resources currently being spent on the complex "rebate economy", where there are often multiple permutations of a rebate, with various complicated administration fees and price protections, leading to costly and labor-intensive calculations by all parties. In a system based on upfront discounts, plan sponsors and payers could shift their selection of PBMs away from looking predominately at rebate levels, and toward overall quality and value. However, both parties will still seek to calculate the impact of an upfront discount on their costs. It is still possible, however, that notwithstanding the initial implementation issues around a system of upfront discounts, once achieved it could offer a system that would be easiest and best for patients while also aligning the business models of the entire drug delivery chain in a beneficial manner.

5.5. A Summary of the Three Alternative Options against Relevant Criteria.

Our summary table is provided on the following page.

Table 5.3. Evaluating Alternative Rebate Models

	Option 1: 100% pass through of rebates to plan sponsors	Option 2: POS rebates for patients	Option 3: Eliminate rebates and move to upfront discounts
Impact on patients' affordability, access to care, and clinical outcomes (via improved adherence)	With less incentive for higher rebates, list prices and gross-net gap may decline, benefiting individual patients financially if their cost-sharing is linked to list price (which could lead to better adherence and outcomes).	Individual patients will see lower costs at the pharmacy counter, which could improve adherence and therefore clinical outcomes. However, the broader enrolled population may eventually face higher premiums.	Patients will have lower cost-sharing based on a discounted list price. Premiums may rise, however, if bargaining power is reduced.
Impact on overall cost of pharmaceuticals and medical spending	May increase rebates returned to plan sponsors but could also reduce incentive for PBMs to seek lowest net price if they are paid flat fees, so impact on overall cost of drugs uncertain. However, the change will impact the MLR which could require reductions in some plan premiums. Would not address the high computational effort and cost associated with the rebate economy.	Transparency of rebates at POS might decrease payer negotiating leverage (but depending on design, confidentiality could be maintained). Increase in plan drug costs because money returned to patients which could lead to premium increases. Overall health costs unlikely to change unless improved adherence drives down non-drug costs. Would not address the high computational effort and cost associated with the rebate economy.	Price concessions may not be as large since they are not linked to moving market share; however, if rebates are currently rarely linked with realized market share, then this disadvantage disappears. Upfront discounts could avoid the costly operational burden of rebate calculation. However, both parties will want to estimate the impact of an upfront discount on their costs.
Impact on competitive outlook for innovative new medicines	No improvement. If plan sponsors receive all rebates, they would have more incentive to favor existing drugs with substantial rebates over new entrant drugs with a single indication. PBMs could offer formularies favoring cost-effective new entrants and allow payers to choose lower list prices or higher list prices with larger rebates.	No direct effect.	New entrants could have improved competitive chances against existing drugs since discounts would not be linked to market share.
Impact on efforts to design formularies based on cost-effectiveness of pharmaceuticals	If 100% pass-through aligns PBM and plan sponsor incentives it could facilitate adoption of value-based formularies based on cost-effectiveness. But post hoc rebates based on utilization make determination of cost-effectiveness within a formulary difficult to assign at product launch. Requires plan sponsors to shift from focus on rebates to value-for-money.	Aligning patient cost-sharing with net price can facilitate the effectiveness of value-based formularies.	Prices are known for formulary design, so provides the easiest platform to construct a value-based formulary based on cost-effectiveness.
Feasibility of implementation	Many PBMs are already offering pass-through options. Transition over time to mandatory model for all PBM-plan sponsor contracts not significantly disruptive.	Although some PBMs are already offering this option, implementation will involve changes in contractual arrangements and information flows.	Potential issues for reconciling the many differently negotiated discounted rates for thousands of drugs along the full supply chain. There is also legal uncertainty about the feasibility of this option.
Ability to improve transparency of costs to support public dialogue on value and affordability	Whilst transparency for payers could be improved if accompanied by clearer dialogue and understanding of rebates, public appreciation of value and affordability unlikely to be affected.	Allowing patients taking a drug to benefit directly from the rebates applied to it is likely to support public dialogue and understanding of value, but likely implementation routes are unlikely to achieve full transparency.	Transparency would be increased, which would support public dialogue on value and affordability. However, it would be possible to implement confidential discounts which would maintain payer bargaining power but not increase transparency of net prices.

6. Discussion

One solution does not fit all

Through our presentation of the three key options, and their assessment against several major considerations, it is apparent that there is no one ideal solution, and that their favorability turns on how one interprets the evidence as well as what can be hypothesized about future scenarios. On top of this, choosing the best policy option will rest on which goals are given the most weight. It is inevitable that stakeholders will vary according to what they most wish to see accomplished.

Whilst efforts to legislate the passing of rebates to payers and/or patients has appeal and is relatively less disruptive, this may not truly tackle the perverse incentive structure and system cost inherent to the rebate economy. Radical change involving the elimination of rebates in favor of upfront discounts has the potential to lead to a simpler system and could more easily facilitate value-based formulary based on cost-effectiveness, but the legal and political barriers to achieving this change are significant.

We have also assumed in our analysis that stakeholders are rational. To the extent that the proposed reforms *could* create a more rational incentive structure, and support a move to lowest net cost (though some contest this), they should be viewed as attractive policy options. However – though it defies logic – a real concern for some plan sponsors is that accounting models have been built around predictable, guaranteed rebates. Whilst this should not guide policy-makers, it may influence the attractiveness or otherwise of any reform in the short-term for some stakeholders.

Transparency versus simplicity and negotiating leverage

The degree of transparency – and the inherent trade-off with negotiating leverage – is rightly in the spotlight. Whilst confidentiality of the negotiated discount or rebate is more challenging to maintain for some options compared with others, for each policy option the level of confidentiality of discount represents a variable design option. There is likely to be a trade-off between transparency and simplicity in particular for options two and three. For POS rebates, decision-makers will need to decide the extent to which members should understand the amount they benefit from rebates, versus how much they want their members to get the most competitive rate based on a confidential negotiation. To maintain confidentiality and avoid back-calculations, patients would need to receive a variable percentage of the rebate at POS, perhaps linked to the average for the therapy class, which would not necessarily improve transparency as compared with the current situation, but should mean that patients pay less at the POS. The interaction between transparency and upfront discounts is also complex. Upfront discounts could be the model that most facilitates use of cost-effectiveness findings in the development of formularies. If the effective price is known at the outset, cost-effectiveness can be determined and compared. Clinicians can more readily become involved in choosing the most cost-effective treatment for their patients. However, it would be preferable for upfront discounts to be able to differ by product, which is likely to require the full level of those discounts to be confidential. The mechanism to achieve this is not clear given the ongoing use of high deductible plan designs in which patients themselves are responsible for the total cost up to a certain threshold. There may even be a trade-off. In the short run, requiring upfront discounts to be transparent may push up costs by reducing negotiating leverage and risking supplier collusion, but in the medium term it may facilitate the use of cost-effective drugs, increasing value for money.

Shortcomings of the proposed options

The overall implications for patient and health system costs for all the options discussed in this paper are not straightforward, and there are various aspects which are not well addressed by any of the proposed solutions. One such aspect is the impact of reform on the competitive outlook of innovative new medicines. In the current rebate system, manufacturers of new medicines with limited indications (and therefore market size) are constrained in the level of rebates they can offer, and therefore disadvantaged in formulary placement. This problem is not addressed by the options presented under rebate reform, but novel ways to address this and promote innovation could include:

- Rebates by indication: rebate volume positioning would only be permitted by indication, meaning that newer innovative drugs targeting a limited number of indications would not be disadvantaged.
- Rebates that do not convey preferred formulary access: decisions would be to include or exclude from the formulary, based on net cost. This would remove the existence of tiers, preferred status, stepped therapy etc., but may also reduce plan leverage to reduce costs.

There is also a completely different approach, which has not been presented explicitly in this paper: a system whereby cost-effectiveness criteria are used to establish a value-based price. With regards the three options presented, this fits most clearly with upfront discounts (the level of discount needs to be decided in some way, and this could be through a value-based assessment), but a more radical option would be to use cost-effectiveness to influence list price directly. To change to a value-based pricing system would represent a radical change to the U.S. system, but could address many of the issues being raised, and obviate concerns around the need to limit access for non-cost-effective drugs.

6.1. What else do we need to know?

There are various research questions that arise from our discussion of the various options. As well as understanding what the potential implications would be of a change to the rebate system, there are also several questions about today's arrangements which – if better understood – could help to offer clarity on the attractiveness of the alternatives. One such key question is:

- To what extent are rebates in the current system linked with utilization?

If they are not, then this eliminates one of the arguments against upfront discounts, which would not allow for discount to be linked with (realized) utilization. Other key questions arising are:

Reforming rebates:

- Would enforcing 100% pass-through of rebates to payers have a meaningful impact, given the trend toward this in today's market already?
- Would POS rebates involve a discount to patients that is significant enough to impact adherence?

- Data and evidence are required on the financial implications of POS rebates for plans; this may need to be mapped out on an individual patient basis, complicating planning efforts.

Replacing rebates:

- What would the Sherman Anti-trust Act mean today for a move away from rebates?
- Is there a way we could have upfront discounts that are known to the payer but not in the public domain?

In addition, for each option there needs to be careful consideration of the differential impact of reform for different payer types. For example, for POS rebates, would the impact on premiums be large enough to impact Medicare Part D coverage? If we eliminated rebates, what would be impact be for those that are most dependent on rebates in the current system (e.g. Medicaid)? How much of the Medicaid rebate is wrapped up in best price versus the inflation protection?

6.2. Conclusion

In this paper we have sought to bring clarity to the reason for the development of the current rebate system, and why it is has become so deeply entwined throughout the drug pricing, coverage, and delivery systems. As noted in the introduction, there are few who do not identify serious shortcomings of the current system. Among these, however, one stands out: that patients who require expensive medications are facing rapidly increasing financial burdens as list prices climb at high rates, even if increases in net prices after rebates are more modest. Rebates on a percent of list price skew the incentives of every single part of the drug delivery chain away from what is best for individual patients and for plan sponsors seeking the most cost-effective approach to providing good health coverage. And innovative life science companies can find that new drugs with superior effectiveness and lower prices still cannot get competitive traction when facing the scale of rebates that the makers of large market-share drugs have at their disposal.

And yet, rebates in their current form have played one essential role: they have given payers some element of negotiating leverage with manufacturers, especially in drug classes with multiple drugs of similar effectiveness. Forcing an abrupt transition away from rebates would raise significant questions about the impact on total costs of care and on patient access and outcomes. Even small effects that would increase health care insurance premiums might have significant effects on individuals who already struggle to afford health insurance for drugs through their employer, health insurance exchange, or Medicare. Any effort at reform should therefore realize the broad effects of any switch to an alternative rebate model. The potential for unintended consequences should be fully realized by policymakers.

Nearly all stakeholders in the health care system realize that some form of change in the traditional paradigm of rebates is needed, and the market has already led important shifts toward 100% rebate pass-through. Early efforts at establishing a POS rebate model to help patients reap the benefits of negotiated prices are also now in play, although it is too early to evaluate the outcomes. Nonetheless, an aspirational target of moving fully toward a system in which upfront discounts could be part of a broader transformation in drug negotiation and delivery is shared by a surprising number of stakeholders. A future health care system whose incentives are fully aligned toward rewarding value while improving access and outcomes for patients will require more radical change than simply giving patients part of the rebate at the POS. We hope this white paper will chasten policymakers who might have seen eliminating rebates or any of the other options as an easy, clean procedure. We equally hope that it will hearten and inform those who wish to take a thoughtful, careful approach to near-term reform while laying the groundwork for a greater transformation to come.

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From: [Sarah Emond](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Attachments
Date: Monday, February 11, 2019 2:43:48 PM
Attachments: [Response to Pioneer paper.docx](#)
[QALY_evLYG_FINAL.pdf](#)

<https://icer-review.org/announcements/icer-describes-qaly/>

The QALY: Rewarding the Care That Most Improves Patients' Lives

Clinicians play a vital role in helping individual patients decide what treatment is best for them. Cost-effectiveness analysis looks at evidence for entire patient populations, comparing the health benefits and economic costs of different treatment options. These analyses are one tool to support broader efforts by governments, private insurers and drug manufacturers to make more transparent, evidence-based coverage policies and pricing decisions. The goal of cost-effectiveness analysis is to help inform policy that will ensure **truly transformative treatments are rewarded handsomely, while neither patients nor society pays too much for care that doesn't offer patients significant benefit.**

The Best Measure of Improved Outcomes for Patients

The Quality-Adjusted Life Year (QALY) is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the U.S. and around the world for more than 30 years.

Creating Incentives to Treat Serious Illness

Because the QALY records the **degree to which a treatment improves patients' lives**, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify a high price. For this reason, ICER has found many innovative and expensive new treatments are highly cost-effective, including:

- ✓ CAR-T for childhood leukemia at \$475,000/treatment
- ✓ Efficizumab for hemophilia at \$450,000/year
- ✓ Personalized lung cancer drugs at \$90,000/year

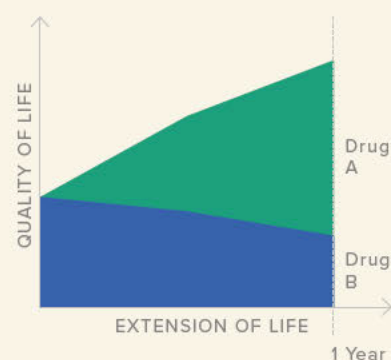
Ensuring Fair Drug Prices, Supporting Better Access

The current drug pricing and insurance system does not work well for patients. The QALY can help. Analyses using the QALY, when embedded in a process guided by patient input and subject to full public discussion, can inform judgments on a fair price of a new treatment. Drugs that make a real difference in patients' lives can be priced accordingly, while lower prices are sought for less-effective treatments. Ultimately, a fair price makes sure that innovative treatments get their due reward, patients and insurers save money when it could be put to better use elsewhere, and patients reap the benefits of broader access to more affordable health care.

HOW THE QALY WORKS

On average, Drugs A & B both extend the lives of patients for one year, but Drug B has severe side effects.

Clinically superior, Drug A is credited with more QALYs gained and, many would argue, deserves a higher price.



I have an incurable blood cancer and rely on pharmaceutical innovation to stay alive. ICER's independent cost-effectiveness analysis—built on the QALY—is one useful input to help us think through what a fair price would be. ICER works to ensure drugs are priced according to the value they bring to patients, which helps us get affordable access to the care we need."

**David Mitchell, President and Founder,
Patients For Affordable Drugs**

Ensuring All Years of Life Are Valued Equally

Concerns have been raised that the use of the QALY could undervalue potential treatments that extend the length of life without improving quality of life for conditions associated with serious illness or chronic disability. This scenario is unlikely and presents little risk of any substantial impact on cost-effectiveness. However, the QALY should always be viewed in a broad context, and to be responsive to these concerns, ICER will highlight an element in our reports that provides policymakers with information that weighs extension of life expectancy equally across all conditions.

The evLYG

ICER's future reports will incorporate more prominently a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures **any** gains in length of life, regardless of the treatment's ability to improve patients' quality of life.

In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community.

Supplementing the QALY, Not Replacing It

To maintain the ability of cost-effectiveness analyses to reflect the full benefits that treatments may have on quality of life, ICER will continue to calculate each treatment's QALY gained. The cost per QALY gained remains the best way for policymakers to understand how well the price of a treatment lines up with its benefits and risks for patients.

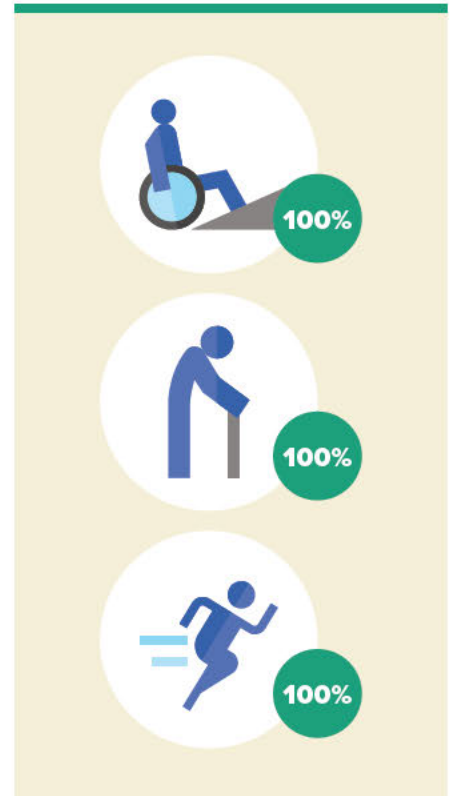
By understanding a treatment's cost per evLYG, as well as its traditional cost per QALY, policymakers can take a broader view of cost-effectiveness and be reassured that they are considering information that poses no risk of discrimination against any patient group. If ICER's analysis finds a major difference in these two measures, we will include specific language in our report describing the underlying characteristics of the treatment and the condition that lead to the difference.

The QALY remains the gold standard in cost-effectiveness analyses for many reasons, and a systematic departure from using the QALY would risk undervaluing treatments that improve the quality of life more than other alternatives for that condition. By drawing greater attention to the analysis of a treatment's evLYG, however, ICER hopes to provide peace of mind to concerned patients and policymakers, while furthering the ability of cost-effectiveness analysis to support explicit, transparent discussions in the U.S. on how best to align a drug's price with its benefits for patients.

ICER'S COMMITMENT TO EQUALITY

ICER's cost-effectiveness assessments compare therapies on their ability to improve quality of life and lengthen life. All reports also will highlight information that values any extension of life **exactly the same** across all diseases, regardless of the patient population's age, severity of illness, or level of disability.

WITH evLYG, ONE ADDED YEAR = ONE ADDED YEAR



ICER welcomes broad stakeholder input on the QALY and the evLYG as we update our value assessment framework in 2019.

Response to Pioneer paper:

Same old time-worn scare tactics: they attempt to paint our efforts to produce an independent evaluation of evidence and think about what a fair price would be as having only one potential outcome: denial of coverage. In fact, the real purpose is to support efforts to get fair prices for innovative treatments to IMPROVE coverage. Our efforts seek to make sure that innovative treatments get their due reward, patients and insurers save money when it could be put to better use elsewhere, and patients reap the benefits of broader access to more affordable health care. In other words: it's not about denial of coverage. It's about getting a fair price that can lead to improved coverage for all patients who can benefit.

Who stands to lose when independent evaluations of cost-effectiveness are used to help inform discussions around fair pricing? Companies that make a lot of money by selling me-too products at high prices or raise prices without any justification, year after year. Companies that make innovative treatments that really benefit patients win. Treatments like CAR-T, successful new treatments for hemophilia, and personalized lung cancer treatments have all demonstrated excellent cost-effectiveness and are examples of how innovative treatments and companies can thrive by getting a fair price linked to patient benefit.

It's not indicated who paid for this report, authored by an ex-Pfizer executive and consultant to drug companies, but it's surprising that Pioneer would take a line that attacks private sector efforts to accomplish what every other developed country does through a governmental process. Attacking private sector answers for societal problems is not usually the Pioneer MO.

Pioneer says in the report that they intend to perform economic analyses of the impact of broad application of cost-effectiveness to pricing on the biotech industry in New England. We would encourage them to broaden their concern and evaluate the economic impact that sticking with the broken status quo on drug pricing would have on patients, families, employers, and state governments trying to maintain budgets for education and other needs.

Errors (there are others as well):

1. "The ICER model caps annual drug spending." It does nothing of the sort. Our methodology explicitly says that our budget impact modeling does NOT imply that drug spending should be capped, it only provides a tool for payers and policymakers to understand when a drug with good long-term value may present short-term affordability concerns, with the goal being pro-active action to make sure that patients do not experience limited access to a high-value drug just because of budgetary concerns.
2. CVS use of ICER reports: "if a drug could not prove a value above \$100,000 it would not be covered." False. In the new CVS benefit design they and other plan sponsors have the OPTION of non-covering if the maker of a non-breakthrough drug demands a price that exceeds a common cost-effectiveness threshold.
3. "For example, the New York State Medicaid program utilized an ICER review to evaluate whether to pay for Orkambi, a breakthrough treatment for cystic fibrosis." False. New York Medicaid used the ICER report as part of a new program approved by the New York state legislature to determine the FAIR

PRICE for drugs when the Medicaid program is exceeding its budget. New York Medicaid officials stated numerous times in public that they would continue to pay for Orkambi and would not consider denying coverage. They only wanted to establish a FAIR PRICE for negotiation with the drug maker who has a monopoly on all treatments for cystic fibrosis.

3. The UK Cancer Drug Fund. All the information in the paper is from 2010. Shortly after the Cancer Drug Fund was established, it was then folded back into NICE so the entire point of the paper is based on old and outdated information.

4. "NICE developed the most prominent methodology cost-effectiveness reviews beginning in the 1970's." NICE was founded in 1999, more than 20 years after the methodological foundation for cost-effectiveness analysis in health care was developed by American health economists and physicians.

5. "The use of the QALY...the United States and Germany have rejected their use." The QALY is used by the CDC and by the ACIP in evaluating childhood vaccinations. It has also been used by the US government in the past to judge fair pricing for HIV drugs.

From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: Re: Gov Baker's Proposal
Date: Monday, February 11, 2019 3:52:20 PM

How about 4pm on Wednesday? What is the best number to reach you at? Alternatively, I can book a conference line.

Sent from my iPhone

On Feb 11, 2019, at 1:47 PM, Hizanishvili, Kaha (EHS) <kaha.hizanishvili@state.ma.us> wrote:

Hi Celia,
Sorry about prolonged silence. It has been really busy. Largely due to the new proposal, actually.
Let's find time to chat this week: I am flexible after 3pm on Tue, Wed or Thu.
Let me know what works on your end.
Thanks,
Kaha

From: Celia Segel [<mailto:csegel@icer-review.org>]
Sent: Tuesday, February 5, 2019 8:06 AM
To: Hizanishvili, Kaha (EHS)
Subject: Re: Gov Baker's Proposal

Hi Kaha,
I am checking in to see if you'd be willing to chat so that we can learn more about Governor Bakers budget proposal on MassHealth. Thanks!
Celia

Sent from my iPhone

On Jan 28, 2019, at 10:13 AM, Celia Segel <csegel@icer-review.org> wrote:

Kaha,
I hope you are well. We were excited to see Governor Baker's proposal last week in his budget about prescription drugs at MassHealth. We'd love to understand the proposal more in detail, and understand what the process is going forward. Do you know who we should talk to?

As an aside, we would truly love your feedback on the final draft of the white paper I sent around late Friday. You brought really important perspective to our meeting, and we've made some fundamental shifts based on your comments (especially with regards to the outcomes-based contracting framing).

Celia Segel

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csegel@icer-review.org
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From: [Hizanishvili, Kaha \(EHS\)](#)
To: [Celia Segel](#)
Subject: RE: Gov Baker's Proposal
Date: Monday, February 11, 2019 1:47:00 PM

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From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: RE: Gov Baker's Proposal
Date: Wednesday, February 13, 2019 4:04:49 PM

That's fine – and no worries. Tomorrow at 4pm works fine. Is there a good number to reach you at?

Celia

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From: Hizanishvili, Kaha (EHS) <kaha.hizanishvili@state.ma.us>
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From: Celia Segel [<mailto:csegel@icer-review.org>]
Sent: Wednesday, February 13, 2019 3:56 PM
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Does it still work to talk in a few minutes? What's a good number to reach you at?

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Director of CER Policy Development

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Two Liberty Square, 9th Floor

Boston, MA 02109

617-528-4013 x7020

csegel@icer-review.org

www.icer-review.org

From: [Celia Segel](#)
To: [Hizanishvili, Kaha \(EHS\)](#)
Subject: RE: Gov Baker's Proposal
Date: Wednesday, February 13, 2019 3:56:28 PM

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From: [Hizanishvili, Kaha \(EHS\)](#)
To: [Celia Segel](#)
Subject: one pager
Date: Thursday, February 14, 2019 4:03:00 PM
Attachments: [masshealth-prescription-drug-pricing-proposal-FY20.pdf](#)

MassHealth Prescription Drug Pricing FY20 H.1 Proposal

January 23, 2019

MassHealth prescription drug spending has nearly doubled from ~\$1.1B to ~\$1.9B since 2012, twice the growth vs. other MassHealth spending.

- Rapid prescription drug cost growth is expected to continue, with high cost drugs as a major driver.
- 20 drugs recently launched or pending FDA approval are expected to cost well over \$100 million annually, after expected rebates.
- Increasingly, new high cost drugs (at times ~\$1 million per course of treatment) are the only drugs in their classes. With no competition for these drugs, MassHealth lacks effective tools to negotiate rebates or cost-effective payment arrangements with manufacturers.

MassHealth maximizes rebates and management of prescription drug costs under current statutory and federal authorities.

- Current State procurement rules restrict MassHealth's ability to directly negotiate with drug manufacturers.
- Under current rules, if manufacturers choose not to negotiate rebates, MassHealth has no recourse.

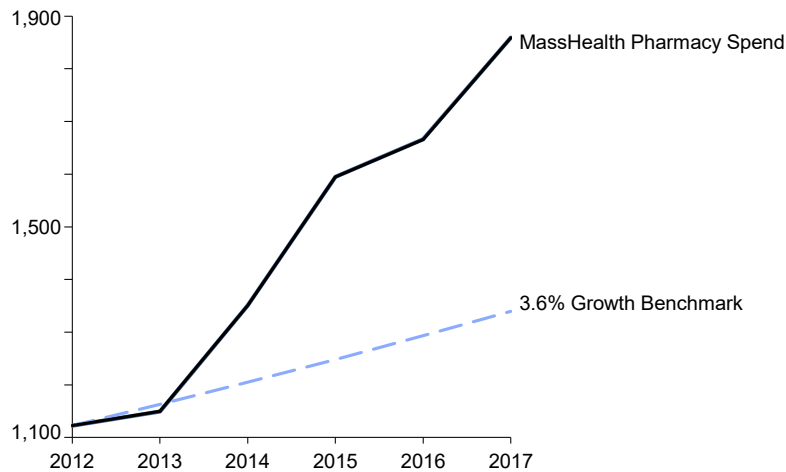
The Baker-Polito Administration's FY20 budget proposes to significantly enhance the tools available for MassHealth to negotiate lower pharmacy prices

- This updated proposal does not include any provisions to exclude drugs from the MassHealth prescription drug formulary.
- It establishes accountability along with transparency of drug prices and incorporates drug manufacturers into public processes that already exist in the state (at MassHealth and the Health Policy Commission) for health care providers and health plans.
- First, the proposal focuses on giving MassHealth greater negotiating leverage for prescription drug prices without impacting access to medically necessary prescription drugs for members. It includes:
 - 1) **Direct Negotiations:** Authorizes MassHealth to negotiate supplemental rebates and cost-effective, outcomes-based contracts directly with drug manufacturers.
 - 2) **Public Process:** If direct negotiations are unsuccessful, MassHealth can establish a target value for a given high-cost drug through a public process, similar to the rate-setting process that exists for most other services that MassHealth covers. MassHealth will seek a supplemental rebate from the drug manufacturer consistent with the publicly determined drug value.
 - 3) **Health Policy Commission (HPC) Accountability Process:** Leverage HPC processes and oversight tools that currently exist for health care providers and payers, to hold drug manufacturers more accountable.
 - If Steps 1 and 2 above are unsuccessful and a drug costs at least \$25K person/year or \$10M in the aggregate annually, MassHealth may refer high-cost drug manufacturers to the HPC. The HPC would be authorized to require manufacturers to submit disclosures and testify at public hearings to justify their prices.
 - 4) **Attorney General's Office:** If the HPC deems the manufacturer's price for a particular drug to be unreasonable or excessive, it may refer the matter to the Attorney General's Office for potential violations of the consumer protection laws.
- Second, MassHealth will also be implementing requirements to limit and make more transparent Pharmacy Benefit Manager (PBM) margins and "spread pricing" within its ACOs and MCOs.

Together, these MassHealth pharmacy initiatives are projected to save the Commonwealth \$80 million net in FY20.

MassHealth Rx spending has nearly doubled over 5 years

MassHealth pharmacy spend
\$ Millions



MassHealth pharmacy reforms: overview of approach

Step 1: MassHealth Direct Negotiations

- Identify highest cost drugs and engage drug manufacturers in direct negotiations to achieve cost-effective, value-based prices

Step 2: MassHealth Public Process

- If no agreement is reached, MassHealth can establish a target value for a given high-cost drug through a public process, similar to the rate-setting process that exists for most other services that MassHealth covers
- MassHealth may amend the proposed target based on public input
- MassHealth will seek a supplemental rebate from the drug manufacturer consistent with the publically determined target

Step 3: HPC Accountability Process

- If no agreement is reached AND the drug meets certain cost thresholds, MassHealth may refer the manufacturer to the HPC for review – consistent with existing statutory frameworks to hold providers and health plans accountable
- The HPC will request disclosures from manufacturers and may require public hearings to defend pricing
- If the HPC deems the price to be unreasonable or excessive, it may refer the manufacturer to the Attorney General for investigation under Chapter 93A

Step 4: AGO

- The Attorney General may investigate the manufacturer under the state's consumer protection law

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To: [Celia Segel](#)
Subject: RE: Gov Baker's Proposal
Date: Thursday, February 14, 2019 3:53:00 PM

Reach me at 617-573-1627.

Talk soon

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Sent: Wednesday, February 13, 2019 4:05 PM
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That's fine – and no worries. Tomorrow at 4pm works fine. Is there a good number to reach you at?

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Sent: Wednesday, February 13, 2019 4:02 PM
To: Celia Segel <csegel@icer-review.org>
Subject: RE: Gov Baker's Proposal

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From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Publishes Final New Evidence Update for Alirocumab, a PCSK9 Inhibitor for Treating High Cholesterol
Date: Friday, February 15, 2019 11:03:04 AM



Institute for Clinical and Economic Review Publishes Final New Evidence Update for Alirocumab, a PCSK9 Inhibitor for Treating High Cholesterol

-- Based on new analyses of published results of the ODYSSEY Outcomes trial, alirocumab would meet cost-effectiveness thresholds if priced between \$2,300 and \$4,000 per year, depending on population --

BOSTON, February 15, 2019 - The Institute for Clinical and Economic Review (ICER) today released a [Final New Evidence Update](#) for alirocumab (Praluent®, Regeneron/Sanofi), an injectable PCSK9 inhibitor used for the treatment of high cholesterol in certain patient populations. This New Evidence Update is based on further analysis of results from the ODYSSEY Outcomes trial, which have now undergone peer review and were [published in the New England Journal of Medicine on November 7, 2018](#).

Based on these new analyses, ICER is revising its value-based price benchmark ranges for alirocumab to \$2,300-\$3,500 per year if used to treat all patients who meet ODYSSEY trial eligibility criteria, and \$2,700-\$4,000 per year if only used to treat higher-risk patients with LDL cholesterol (LDL-C) = 100 mg/dL despite intensive statin therapy. ICER's value-based price benchmarks suggest a price range, net of any discounts and rebates, that aligns fairly with the treatment's added benefits for patients and the health care system. The ranges reflect commonly cited cost-effectiveness thresholds of between \$100,000 and \$150,000 per Quality-Adjusted Life Year (QALY) gained.

This Final New Evidence Update is the revised version of ICER's [preliminary analysis](#) of the ODYSSEY Outcomes data initially presented at the American College of Cardiology's 2018 Scientific Session. Consistent with the [methodology](#) defined on our website, we are now updating that analysis based on the final trial data published in the peer-reviewed manuscript. Of note, Regeneron and Sanofi announced recently that the annual US list price of alirocumab would be reduced to \$5,850, down from \$14,600 when the drug was first launched in 2015.

"When added to maximally tolerated statin therapy in patients with a recent acute coronary event and an LDL-C of 70 or higher, alirocumab reduced cardiovascular

events by 15% and appeared to reduce all-cause mortality by a similar amount," said David Rind, MD, ICER's Chief Medical Officer. "In our preliminary update we had interpreted the evidence as suggesting that the relative reduction in events is greater in patients with an LDL-C above 100 mg/dL. Having reviewed the full published information, however, we now believe it is more likely that the relative benefit of treatment is the same for all patient groups, and thus our updated value-based price benchmark for the high-risk subgroup is lower in this final report than in our preliminary analysis. Some experts, however, continue to believe the evidence supports a higher relative benefit for high-risk patients, and therefore we have included in our final report a supplemental scenario analysis based on this alternative assumption."

ICER's value-based price benchmarks remain lower than even the recently reduced list price of alirocumab. Under the scenario analysis that assumes greater relative benefit in patients with LDL-C above 100 mg/dL, the value-based price benchmark range for the high-risk subgroup would be \$4,900-\$7,400 per year.

This analysis was conducted in partnership with an independent research group led by Dr. Kirsten Bibbins-Domingo at the University of California, San Francisco and Dr. Dhruv Kazi at the Beth Israel Deaconess Medical Center. The team used the Cardiovascular Disease Policy Model, an established simulation model of cardiovascular disease (CVD) in the US population that systematically combines data from vital statistics, epidemiologic studies, clinical trials, and registries.

ICER's Earlier Assessments of the PCSK9 Inhibitors

ICER [first assessed](#) the cost-effectiveness of alirocumab and evolocumab (Repatha®, Amgen) shortly after these drugs were first granted regulatory approval in the US in 2015, and performed a [New Evidence Update](#) for evolocumab in September 2017, following the release of outcomes data from the FOURIER trial. This Final New Evidence Update is the revised version of ICER's [preliminary analysis](#) of the ODYSSEY Outcomes data initially presented at the American College of Cardiology's 2018 Scientific Session. Today's announcement does not alter ICER's analysis of the FOURIER trial, which concluded that a value-based price benchmark for a year's treatment with evolocumab would be between \$1,700 and \$2,200.

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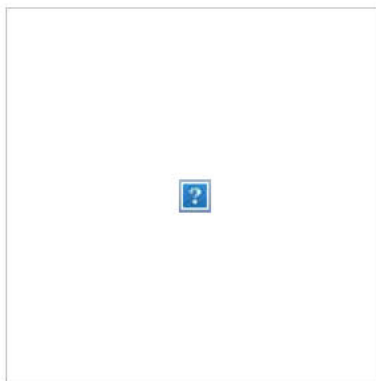
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From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER Weekly View: February 15, 2019
Date: Friday, February 15, 2019 7:23:03 AM



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[ICER Weekly View: February 15, 2019](#)

From the desk of David Whitrap

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- Different options for lowering drug prices internationally, in the US, and in each state;
 - How certain manufacturers are beginning to lower list prices voluntarily, and what that means for the rest of the industry;
 - The positive recommendation a depression treatment just received from the FDA Advisory Committee; and
 - Some concerning new findings about manufacturers influencing physicians' prescribing habits.
-



From value-based pricing, to reference pricing, to tendering, the World Health Organization recently detailed several methods other countries are currently using to achieve lower drug prices than what we pay in the US.

[How other countries set their drug prices \(Axios\)](#)

And if you tuned into the multiple drug pricing hearings that occurred over the past two weeks on Capitol Hill, you saw how the new Congress is considering how some of these techniques could be applied in the US. Perhaps of particular interest to recipients of this newsletter, there's the proposed idea of Medicare negotiating toward a "third price based on independent research."

[Liberals worry Pelosi may pivot away from a bold drug price plan \(Politico\)](#)

But it looks like California, like several other states, isn't waiting for federal action to slow rising drug costs.

Can California Beat The Federal Government In Lowering Drug Prices? **(Kaiser Health News)**

Some forward-thinking life science companies are getting ahead of the curve, too. This week, Regeneron and Sanofi announced they would lower the US list price of their PCSK9 inhibitor Praluent to \$5,850 per year, matching Amgen's similar reduction for Repatha.

Matching Amgen, Regeneron to Cut List Price of Heart Drug by 60% **(Xconomy)**

This sort of voluntary reduction of the list price might complicate matters for certain members of the supply chain. There are new reports that the pharmacy benefit manager OptumRx is asking manufacturers to keep rebates consistent, even if list prices are lowered.

A big PBM wants drug makers to agree to rebate demands that would preserve its bottom line (STAT News)

Ahead of [ICER's assessment](#), the FDA Advisory Committee had a near-unanimous vote to recommend approval of esketamine for the treatment of depression.

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A new analysis finds that oncologists who receive payments over an extended period of time - mostly for speaking or consulting - are much more likely to prescribe a medicine made by the company that writes them a check. And the effect was seen even among physicians who only accepted \$100 per year.

Drug company payments for consulting and speaking influence oncologists' prescribing (STAT News)

And to wrap things up this week, I think this one speaks for itself:

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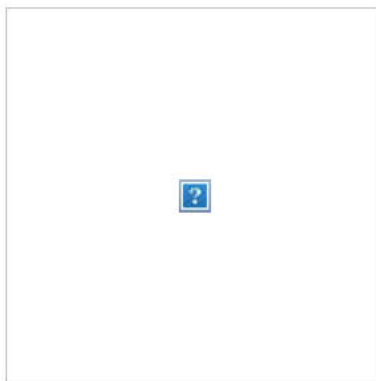
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Sent by info@icer-review.org

From: [Matt Seidner](#)
To: [Matt Seidner](#)
Subject: ICER: revised SMA report delayed to Friday
Date: Wednesday, February 20, 2019 12:11:34 PM

Dear New England CEPAC,

We've decided to delay the publication of our revised Evidence Report on Spinraza and Zolgensma for SMA by one day – the report will now be issued on Friday, 2/22. This shift won't impact any of the remaining key dates for the review. My apologies for any inconvenience this may have caused, and please feel free to reach out with any questions or concerns.

Best,

Matt Seidner

Program Director
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From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER to Publish Upcoming Assessment on Additive Cardiovascular Disease Therapies
Date: Friday, February 22, 2019 2:26:51 PM



Institute for Clinical and Economic Review to Publish Upcoming Assessment on Additive Cardiovascular Disease Therapies

-- Report will be subject of Midwest CEPAC meeting in September; Open Input now being accepted until March 12, 2019 --

BOSTON, February 22, 2019 - The Institute for Clinical and Economic Review ([ICER](#)) announced today that it plans to assess the comparative clinical effectiveness and value of icosapent ethyl (Vascepa®, Amarin Pharma) and rivaroxaban (Xarelto®, Janssen Pharmaceuticals), additive cardiovascular disease (CVD) therapies. The report will be reviewed during a public meeting of the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)) in September of 2019.

ICER's website provides [timelines of key posting dates and public comment periods for the assessment of additive CVD therapies](#). An Open Input period begins today and is intended to allow stakeholders to share key information relevant to the development of the evidence report. Comments will be accepted from all interested stakeholders until March 12, 2019 at 5pm ET. During this time, ICER will also contact key patient groups and clinical experts to gain further insights on the patient perspective and clinical context of treating CVD.

For more information about the Open Input period, visit [ICER's website](#). ICER's [Manufacturer Engagement Guide](#), [Patient Participation Guide](#), and [Patient Guide to Open Input](#) provide additional information for manufacturers and patient groups, including an explanation of what types of information may be most informative. There are no page limits to Open Input submissions, and input received will be incorporated throughout report development. All input can be emailed to publiccomments@icer-review.org and must be received by 5 PM ET on March 12, 2019 to be considered.

A draft scoping document, which will provide more detail on ICER's planned analysis, will be available on March 18, 2019. That document will be open to public comment for three weeks.

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website](#).



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To: [Lenz, Kimberly \(EHS\)](#)
Subject: ICER to Publish Upcoming Assessment on Additive Cardiovascular Disease Therapies
Date: Friday, February 22, 2019 2:26:56 PM



Institute for Clinical and Economic Review to Publish Upcoming Assessment on Additive Cardiovascular Disease Therapies

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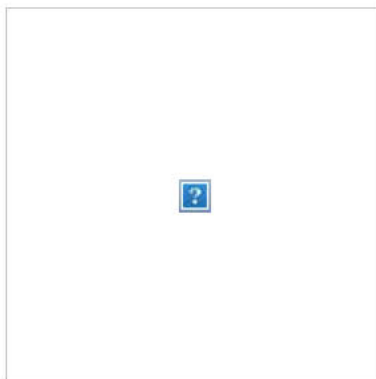
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[ICER Weekly View: February 22, 2019](#)

From the desk of David Whitrap

Hello, everyone. It's a busy day here at ICER. In addition to releasing our revised Evidence Report on treatments for spinal muscular atrophy later this afternoon, we will also announce the topic for our next drug assessment. Stay tuned...

But this morning, let's take a look at:

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 - **Pharmaceutical News:** CAR-T in Medicare, spending trends over the next decade and the financial toxicity that could follow, Maryland's failed bid to prohibit "unconscionable" price gouging, the long backstory on how the insulin market became so entrenched, what to expect next week when pharma execs go to Washington, and a trio of industry kickbacks.
-



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Earlier this week, analysts from Morningstar alluded to ICER's value-based assessments as one of several factors that are placing drug companies under more pressure to think differently about how they price their products. The analysts went on to write: *"Given the pricing pressure overhang, firms need higher levels of innovation in their pipelines to justify pricing... Slight dosing advantages and minor improvements in efficacy in crowded therapeutic areas will not support the innovation needed for pricing power as was the case in the*

1990s and early 2000s."

Pfizer, Merck, J&J well-positioned for M&A and Biogen and BioMarin are prime targets (FiercePharma)



Fair drug prices should result in both fair access and incentives for future innovation. Remember last year when [ICER's assessment](#) concluded that the CAR-T therapies Kymriah and Yescarta were cost-effective despite prices that approached \$500,000? And remember how we recommended that all patients be entered into a registry for planned long-term follow-up? Well, CMS is now proposing that Medicare cover all FDA-approved CAR-T therapies as long as data is collected about how the patients fare for at least two years following treatment.

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Even without any further expansion of Medicare or Medicaid, new estimates suggest that government will be paying for nearly half of the nation's health care in less than 10 years. And during that same timeframe, prescription drug spending is expected to rise 6.1% each year.

Government headed for close to half of nation's health tab

(The Associated Press)

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U.S. top court rejects Maryland bid to revive drug price-gouging law
(Reuters)

And speaking of essential medicines that have been available for years, do you ever wonder how the \$27 billion annual market for insulin has been dominated by only three companies over an entire century? Several policy experts spoke with STAT News about how we got here, and options the government could consider to spur additional competition. *(And it's always nice to see older ICER reports helping inform conversations like these.)*

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[The fighter, the saint, and the odd man out: the executives who will defend pharma before Congress](#) (STAT News)

And finally, this week brings a collection of stories about three different types of industry kickbacks that can create conflicts of interest that ultimately increase health costs. Alexion becomes the latest pharmaceutical company to settle after being accused of using patient assistance programs to illegally cover Medicare patients' out-of-pocket expenses. Gilead is accused of funneling money to physicians through programs that helped boost sales of the company's hepatitis C and HIV drugs. And ProPublica unpacks how the lucrative commissions insurers pay brokers may represent a perverse incentive that could lead to increased premiums.

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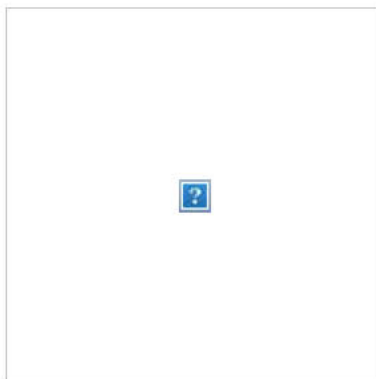
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To: [Laura Cianciolo](#)
Cc: [Matt Seidner](#)
Subject: ICER: Evidence Report
Date: Friday, February 22, 2019 12:21:52 PM
Attachments: [ICER SMA Response to Comments 022219.pdf](#)
[ICER SMA Meeting Agenda 030719-01.pdf](#)
[ICER SMA Public Comments 022219.pdf](#)
[ICER SMA Evidence Report 022219.pdf](#)
[ICER SMA Revised Voting Questions 022219.pdf](#)
[ICER SMA Voting Worksheets 022219.pdf](#)

Dear New England CEPAC Council,

I hope you're all doing well. I'm writing to provide the Evidence Report *Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value*. I've also attached the voting questions/worksheets, meeting agenda, public comments, and our responses. Let me know if you don't receive any of these due to file size limits, and I can send them in a separate email.

Please feel free to reach out with any questions about the report or meeting. I look forward to seeing you all next month!

All the best,
Laura

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**Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value
Response to Public Comments on Draft Evidence Report**

February 22, 2019

Table of Contents

Manufacturers	2
AveXis	2
Biogen	7
Genentech	14
Clinicians and Health Economists	17
Richard Finkel, MD	17
Louis Garrison, PhD	17
Patient Advocacy Groups	18
Cure SMA	18
Muscular Dystrophy Association	21
Patients Rising Now	22

#	Comment	Response/Integration
Manufacturers		
AveXis		
1.	<p>1. We disagree with ICER's base case model assumption that 1/6 of sitting ZOLGENSMA patients return to the not-sitting state at the end of the short-term model, and with ICER's assumption that these patients "required" Spinraza. This assumption is not grounded in evidence and is inconsistent with those made for Spinraza. We acknowledge scenario analysis #6 reports results assuming no loss of milestones, and removing this assumption lowers the ICER by \$17,000 to \$230,000 per QALY for ZOLGENSMA vs. BSC. However, we request the modeling team remove this loss of sitting milestones assumption for ZOLGENSMA in the base case. We also request the removal of the word "required" when referencing patients who did receive Spinraza after ZOLGENSMA as there is no evidence to support this language.</p> <ul style="list-style-type: none"> • There is no clinical evidence to support the milestone loss. Importantly, no patients who received the therapeutic dose in the ZOLGENSMA CL-101 24-month study, or the long-term study (maximum follow-up of 30 months) experienced any loss of milestones or worsening disease. • There is no evidence that Spinraza was "required" or beneficial for ZOLGENSMA patients in the trial. It is highly implausible that any ZOLGENSMA-treated patient would receive additional benefits by commencing chronic treatment with Spinraza. • Because there was no evidence of clinical deterioration in the CL-101 trial, it is our contention that the decision to initiate Spinraza post ZOLGENSMA was driven by parental desire, rather than by clinical indication or biological plausibility. It is understandable that parents would have considered additional options, regardless of the lack of scientific evidence to support the plausibility of additional effectiveness (see above). And, while the specific motivations that underlay the decision to initiate use of Spinraza is a private matter between patient's guardians and physician, these motivations should not be used as a foundational assumption that patients were deteriorating or that Spinraza was required. 	<p>Clinical expert opinion suggested that both rationales for seeking Spinraza were plausible (i.e. patients seeing benefit on Zolgensma but wanting to achieve additional benefit, and patients losing milestones who want the therapy to prevent further loss). As such, we assumed that half of the patients on Spinraza would lose a milestone. We have amended the text to state "apparently required" Spinraza. We note the new data presented the counterfactual is still unknown.</p>
2.	<ul style="list-style-type: none"> • ICER's approach to ZOLGENSMA milestone persistence, which was modeled as a decline in the absence of evidence, is contradictory to ICER's approach to Spinraza milestone persistence, which was modeled as consistent despite published data showing a decline in the proportion of sitting patients. Table 4.2 (page 56) of the ICER report states: "In the short-term model for Spinraza, we assumed that the numbers of patients sitting cannot decrease over 	<p>We have updated the short-term data on the proportion sitting in Spinraza arm (please see Appendix E2), which does not include the persistence assumption in the short-term model.</p>

#	Comment	Response/Integration
	<p>time.” This is explained in Table E2 and page 158: The numbers of patients sitting are monotonically increased with time, except for the last time point where the number of patients sitting is lower than the previous time point. It is not clear if this is due to administrative censoring or patients losing milestones. We assumed that this was due to administrative censoring, and in step three, the number of patients sitting at the last time point was set as equal to those in the previous time period.” This assumption’s importance can be observed in the one-way sensitivity analysis for Spinraza (Figure 4.4, page 72), Scenarios 7a-c for Spinraza vs BSC (Table 4.21, page 75), and where ICER reports 64% of Spinraza QALYs are from the sitting (Table E12, page 168).</p>	
3.	<ul style="list-style-type: none"> • The loss of milestones assumption was not mentioned in the original model analysis plan. Based on the report, it is unclear whether clinical, SMA or gene therapy experts were consulted about this assumption, and a discussion with experts or AveXis may have benefitted this assumption. • If the assumption is not removed, for the purposes of balancing the analysis, we request the modeling team conduct a scenario analysis where responders are restored to full health. 	<p>The loss of milestones was discussed with a clinical expert. The observed data apparently shows that none of the patients who received Spinraza after Zolgensma achieved full health and thus this scenario analysis has not been conducted.</p>
4.	<p>2. We request the modeling team conduct a new value-based price (VBP) analysis for the threshold prices in Table 4.26 using the “no milestones lost” assumption for ZOLGENSMA.</p>	<p>The value-based price analyses for threshold prices will only be conducted for the base-case model.</p>
5.	<p>3. As discussed in earlier consultations, we recommend ICER’s “Report at a Glance” should include all relevant thresholds including the VBP analysis using a willingness-to-pay of \$500,000 per QALY. This short version report is more accessible for decision makers than long-form reports, and including this figure would be consistent with ICER’s stated objectives for ultra-rare diseases. This request is also supported by a £100K- £300K per QALY threshold for ultra-orphan drugs by NICE.</p>	<p>While our threshold prices extend to the \$500,000 per QALY threshold for reviews conducted under ICER’s ultra-rare disease framework, our value-based price benchmarks are still the prices that would meet the \$100,000 to \$150,000 per QALY threshold. We always publish the value-based prices (and not the entire range for threshold prices) in the “Report at a Glance” document.</p>
6.	<p>4. We find the “ZOLGENSMA vs Spinraza” scenario (Pages 77-8, Tables 3, and 4.23-24) misleading.</p> <ul style="list-style-type: none"> • We recommend this scenario should be removed given the lack of clinical and biologic plausibility for sequential treatment with Spinraza (Point 1), and an unaddressed uncertainty of whether Spinraza would be covered for ZOLGENSMA-treated patients by US insurers. • If this scenario is not removed, we request the scenario be relabeled as “ZOLGENSMA followed by Spinraza vs. Spinraza” for clarity, as this reflects the true comparison. • Further, it would be appropriate for ICER to modify the scenario and report the scenario where ZOLGENSMA 	<p>We believe this scenario addresses an important policy consideration and will help inform decision-making, so have not removed it from the revised report. In our description of this scenario, we have explicitly stated that Spinraza is added on to Zolgensma for a percentage of patients in the Zolgensma arm.</p>

#	Comment	Response/Integration
	<p>(monotherapy) is the comparator against the sequential treatment. The current ICER of \$202,000 (Table 4.23, page 78) shows the incremental benefit of ZOLGENSMA as a bridging therapy to Spinraza treatment, an indication for which ZOLGENSMA has not been studied, nor follows clinical rationale. ZOLGENSMA as the comparator shows the incremental benefit of adding Spinraza post-ZOLGENSMA. Based on current values in the reports, we have calculated this ICER for ZOLGENSMA followed by Spinraza vs ZOLGENSMA to be \$1,415,323/QALY $((\\$5,240,000 - \\$3,485,000) / (12.57 - 11.33) = \\$1,755,000 / 1.24)$. Adding Spinraza to ZOLGENSMA-treated patients would not be clinically justified nor cost-effective.</p> <ul style="list-style-type: none"> • We also request the modeling team report an additional scenario analysis of "ZOLGENSMA monotherapy (without milestone loss) vs. Spinraza monotherapy" so that the committee, and subsequent audiences, can more fully consider the long-term value for money. • In the event ZOLGENSMA followed by Spinraza vs. Spinraza scenario is not removed, based on recent data from the ZOLGENSMA managed access program (MAP) (16 out of 20 =80% MAP patients received Spinraza prior to ZOLGENSMA), we request ICER to conduct a switch strategy scenario (1 to 3 doses of Spinraza followed by ZOLGENSMA) and report the ICERs for switch strategy vs. BSC and Spinraza monotherapy." 	
7.	<p>5. To match current recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine, NICE, and HTA agencies in The Netherlands and Belgium, and given the long-term health benefits provided by ZOLGENSMA, we request the modeling team conduct additional scenario analyses using differential discounting (i.e., 3% for costs and varying utilities from 0% - 3%). Also, as recommended by the Second Panel, we request that the modeling team include discounting as part of the one-way sensitivity analysis for all treatments.</p> <p>There is broad agreement that in cost-effectiveness analysis (CEA), future outcomes should be discounted, and their present values calculated so that cost-effectiveness ratios will be appropriately adjusted for the differential timing of costs and consequences. However, there is disagreement over the appropriate discount rate to use. The Second Panel noted that the appropriate discount rates for costs and health will depend, among other things, on fixed health care budgets, the social objective of maximizing welfare vs health, and social time preferences (which may be different for health vs consumption). The Second Panel recognized the uncertainty around the</p>	<p>We have now included a scenario analysis using a 1.5% discount rate. We have also included undiscounted costs and outcomes for the base-case analysis in the appendix.</p>

#	Comment	Response/Integration
	<p>appropriate discount rates from societal and health care sector perspectives. The Panel noted that “since the goal of the Reference Cases is to promote comparability across studies, we recommend that a 3% interest rate be used for both costs and effectiveness from both the societal and the health care sector perspectives.” We recognize this rate was used in the ICER model. However, the Second Panel stated it is always advisable to perform sensitivity analyses for any baseline discount rates used, especially when the costs and benefits are incurred at different times for different interventions. More recently, other have argued, based on theoretical and empirical evidence, that the Second Panel’s recommended discount rate of 3% per annum is too high, resulting in systematic bias against health technologies with upfront costs and long-term health effects.</p>	
8.	<p>• We note ICER is preparing its framework for curative therapies and hope ICER will consider the merits of differential discounting in its assessment. As the standard practice in the US is to discount benefits at the same rate as costs, the benefit of potentially curative medicines may be severely misrepresented. In the meantime, given the considerable public attention to ICER reports beyond the field of health economics, it would be beneficial to patients and members of the public for an undiscounted survival benefit to be published, as well as a VBP based on undiscounted benefits. This is demonstrated well by an example from the published draft report. Table E10 (page 167) reports a gain of 32.4 undiscounted life years for the ZOLGENSMA cohort. To test the ICER per QALY, we multiplied the corresponding utility value for each health state (using 0.88 as an average for walking) by the undiscounted LYs (by health state) for ZOLGENSMA to yield the undiscounted QALYs. Our calculations show ZOLGENSMA yields 22.4 undiscounted QALYs; in the base case (3% discounting) ZOLGENSMA yields 11.33 QALYs. Removing discounting nearly doubles the QALYs. Using costs from Table 4.13 (page 70) shows the benefit of differential discounting (3% costs, 0% utilities), as the ICER for ZOLGENSMA vs. BSC lowers to \$123,000 / QALY from the base case of \$247,000 / QALY.</p>	<p>We are researching and evaluating the merits and disadvantages of differential and variable discounting in models that include curative therapies as part of our "valuing a cure" project. Since that effort is ongoing and is not complete yet, we feel it premature to include differential discounting in this assessment. We have, however, now included a scenario using a discount rate of 1.5% per annum, and included undiscounted outcomes and costs for all interventions assessed. Results of the latter can be found in the appendix of the report.</p>
9.	<p>6. We appreciate HTA bodies outside the US frequently use stopping rules in CEA. We disagree with the base case 24-month stopping rule assumption for Spinraza, as this is not likely to be indicative of US clinical practice. We request that the modeling team report the results from scenario analyses where different Spinraza stopping rules are tested (e.g. 36 months, 48 months).</p> <p>• Insurance guidelines for Spinraza suggest that Spinraza</p>	<p>Given the contradicting suggestions from the different stakeholders regarding this issue, we are keeping the 24 month stopping rule for the patients who do not achieve milestones.</p>

#	Comment	Response/Integration
	can be continued if it helps to improve, maintain, or slow the disease progress. Spinraza is indicated for life-long treatment. Therefore, even if patients do not achieve a milestone (i.e., not sitting to sitting), it is expected that they would continue treatment. Understanding how the stopping rule affects the Spinraza vs. BSC ICER results will be important when assessing long-term value for money.	
10.	7. We request the modeling team remove the "Drug X" pre-symptomatic analysis. We enthusiastically agree that there is promise for treating SMA patients early. However, there is little clinical evidence to support these analyses, thus the "Drug X" analyses are premature and speculative. Also, as the results rely heavily on patient mix, they are not generalizable. The patient mix does not match the ongoing pre-symptomatic study AveXis is conducting which means ICER's results are unlikely to reflect how ZOLGENSMA will be used in practice. Further, it is unclear how SMA patients may be identified pre-symptomatically as not every US state has a compulsory newborn SMA screening program. Therefore, the source and validity of pre-symptomatic prevalence assumptions are unclear.	As SMA screening programs become increasingly prevalent, we anticipate that Zolgensma (and/or other gene therapies) will be used in pre-symptomatic SMA patients. Therefore, we found it necessary to model and understand the implications on the potential value of a therapy in this population if it were priced and had the same efficacy of Zolgensma in the SMA Type 1 population. We acknowledge that the trial for Zolgensma in this patient population is ongoing and there exists no other published evidence on its efficacy in this sub-population. We have thus named the potential therapy "Drug X" and not Zolgensma.
11.	8. We request optimistic versions of scenarios 7a-7c (i.e., assume 10/20/30% of sitting [or not sitting] patients transition to walking [or sitting] at the end of the short-term model) to test uncertainties.	We feel the base case model is already optimistic as we assume that the motor function milestones are sustained until death.
12.	9. We request the modeling team conduct a scenario analysis accounting for a blended Spinraza price: 60% with \$127,500 (Table 4.7, page 66) and 40% with the hospital markup ranging from 8% to 60%. In Table 4.7, ICER assumes no hospital markups for Spinraza. However, in calculating the total administration cost for Spinraza, ICER assumes 40% of patients receive Spinraza in inpatient settings (Table 4.8, page 5). If 40% of patients receive Spinraza in inpatient settings, it would be reasonable to account for the hospital markup costs for Spinraza. Our range recommendation is from clinical experts who have advised hospital markups could range between 8%-60% per dose.	The base-case analysis already includes the hospital markups (please see Table 4.7).
13.	10. Intubation in the US is more common. We request ICER conduct a scenario using pooled survival curve of non-invasive and tracheostomy patients (PV to death) with a survival limit (e.g. 22 years).	We do not feel that conducting this scenario analysis is necessary.
14.	11. There are several important considerations for ZOLGENSMA that should be added to Section 5 – Potential Other Benefits and Contextual Considerations. We list these below. • ZOLGENSMA is a one-time, one-hour IV treatment that should eliminate patient and caregiver anxiety,	Thank you for noting these important considerations. They have been added to Section 5.

#	Comment	Response/Integration
	<p>inconvenience, and complexity associated with repeated lumbar punctures needed for Spinraza while improving patient outcomes.</p> <ul style="list-style-type: none"> • The benefits of ZOLGENSMA extend beyond improved patient survival and quality of life. These children will have the potential to attend school and require substantially reduced levels of care, allowing family to return to work, with subsequent mental health and financial benefits. • Due to its mode of action and its one-time dosing, ZOLGENSMA may reduce the existing burden on caregivers by helping to eliminate the need to continuously navigate complex and often-changing health insurance coverage policies. 	
Biogen		
1.	<p>(1) The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings.</p> <ul style="list-style-type: none"> • Page 51: The rationale for assigning investigational AVXS-101's uncontrolled, single-site, open-label Phase I CL-101 trial, which enrolled only 12 patients in the proposed therapeutic dose cohort, an evidence rating of an "A" is unsubstantiated. The ranking of CL-101 in infantile-onset SMA eliminates the large difference in evidence between investigational AVXS-101 and the robust Spinraza clinical trial data. As stated by ICER on Page 51: "Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A)." According to ICER's evidence rating matrix, an "A" rating requires high certainty in level of evidence and a substantial comparative net benefit effect. In reference to investigational AVXS-101, we believe that the net health benefit is currently uncertain, particularly given lack of data on the durability of investigational AVXS-101. The long-term efficacy of investigational AVXS-101 is unknown, with data limited to a single-site, open-label, uncontrolled study of a small population of infants with SMA treated for just over 24 months as of the last report. Furthermore, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended. ENDEAR, a randomized, multi-center, international, double-blind, sham-controlled Phase III study, with a total of 121 participants, should not receive the same rating as an uncontrolled trial with only 12 participants. Furthermore, patients with infantile-onset SMA who were treated with Spinraza in ENDEAR have been followed for nearly 3 years 	<p>We have added a section to the report explaining the rationale behind the evidence ratings and the differences in the evidence bases for Spinraza and Zolgensma.</p>

#	Comment	Response/Integration
	in the SHINE extension study, during which additional improvements in motor milestones and general motor function have been observed.	
2.	<ul style="list-style-type: none"> • There were two patients (N=2/12 or 17%) in the high dose cohort of CL-101 who were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]). This raises questions on the sponsor's ability to select appropriate patients for an SMA Type 1 study and why these two patients were included in the proposed therapeutic cohort. • Page 25-26: 17 out of 19 publications meeting PICOTS criteria were Spinraza studies, which points to its solid evidence base while also underscoring the prematurity of the ICER analysis of investigational AVXS-101. • An ICER report from October 2018 assigned a "C+" rating to the evidence for investigational inotersen for hereditary transthyretin amyloidosis (hATTR) based on NEURO-TTR, a Phase III, randomized, controlled trial with 172 total patients followed for over 15 months after treatment. Similarly, in a report from February 2018, ICER assigned a "B+" rating to voretigene neparvovec for biallelic RPE65-mediated retinal disease, based in part on a Phase III randomized control trial (Study 301) with 31 participants. This represents a large inconsistency in ICER evidence ratings across evaluations. 	Both patients were genotyped and genetically confirmed to have SMA and two copies of <i>SMN2</i> . Both showed symptoms of disease onset prior to six months of age as required by the trial inclusion criteria.
3.	<p>2. ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101.</p> <ul style="list-style-type: none"> • Although ICER did not assign an evidence rating comparing investigational AVXS-101 versus Spinraza for infantile-onset SMA in the Comparative Clinical Effectiveness section of its report (Section 3.5), the foundation of ICER's economic modeling in Section 4 is the clinical data, for which ICER makes no adjustments to account for differences in baseline characteristics between study populations, as recommended by ISPOR's Good Research Practices. • Page 51: ICER notes "Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of investigational AVXS-101 versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I)." • Page 31: Key baseline characteristics of ENDEAR and CL-101 indicate that the patient populations have clinically 	As explained in the draft report, adjusting for differences in baseline characteristics is not possible without access to individual patient data. We have requested this analysis from Biogen multiple times without success. As such, we have acknowledged this issue of naive comparison in our report (please see Table 4.2).

#	Comment	Response/Integration
	<p>relevant differences, with patients in ENDEAR having a comparatively less favorable profile in terms of potential to respond to therapy:</p> <ul style="list-style-type: none"> o Treatment with Spinraza was initiated later after disease onset compared to investigational AVXS-101: Patients treated with Spinraza in the ENDEAR study (mean age: ~5.3 months) were older at study initiation compared to investigational AVXS-101 patients in the high dose cohort of CL-101 (mean age: ~3.4 months). o Patients treated with Spinraza in the ENDEAR study had a longer disease duration (3.3. months) compared to patients treated with investigational AVXS-101 in the high-dose cohort of CL-101 (approximately 2.0 months). o There was a greater proportion of patients treated with nusinersen in the ENDEAR study (26%) who required respiratory intervention at baseline than those in the high-dose cohort of CL-101 (17%), which could have an important impact on clinical outcomes, such as event-free survival and respiratory outcomes. Table 3.1 incorrectly transposes numbers from those reported in Table 1 of the Mendell et al 2017 publication. <p>Page 36: As noted in the previous point, two patients (N=2/12 or 17%) in the high dose cohort of CL-101 were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]). Due to early treatment and higher baseline motor function, these patients may have had more opportunity to respond compared to patients treated with Spinraza in ENDEAR who received initial treatment at a later age and had lower baseline motor function.</p> <p>Page 78: Of great concern, ICER estimates an incremental cost-effectiveness ratio comparing Spinraza and investigational AVXS-101 in the infantile onset patient population based on a naïve, unadjusted comparison of trial data. In contrast, HTA bodies such as NICE in the UK and the TLV in Sweden are cautious to conduct such cost-effectiveness evaluations based on naïve comparisons and ask for adjusted comparisons also in areas where such comparisons are challenging to conduct, as exemplified by their evaluations of CAR-T therapies such as Yescarta and Kymariah.</p>	
4.	Lack of consensus exists on appropriate methods to assess the substantial uncertainty around long-term safety and effectiveness of gene therapies.	We agree that a lack of consensus exists in the appropriate methods to address the long-term effectiveness and safety of gene therapies. We

#	Comment	Response/Integration
	<p>In the absence of a consensus on appropriate methodology, ICER should utilize durability assumptions for its evaluation of investigational AVXS-101. One consideration would be to use what was previously applied for durability assumptions for the gene therapy voretigene neparvovec for inherited retinal disease. In this previous assessment, treatment effect was assumed to be maintained for 10 years, followed by a 10-year waning of effect, after which the rate of decline in vision was the same as SOC. There are significant unknowns in the long-term efficacy of investigational AVXS-101, further amplified by the extremely limited number of patients who have received this treatment to date. In addition, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended.</p>	<p>have now included a scenario analysis using a shorter time horizon of 10 years.</p>
5.	<p>In either the base case analysis or in the scenario analyses, ICER should assume that SMA patients treated with Spinraza will continue to improve (e.g., increase motor function) as observed in clinical trials results, such as the ENDEAR/SHINE analysis, and reports from real-world practice. In ICER's current analysis, improvements observed in clinical trials and real-world practice are ignored and replaced with the incorrect assumption that patients do not improve from the health state they are in at the end of short-term clinical trials.</p>	<p>Strong evidence of continued improvement has not been presented. The base case, which uses differential utility between Spinraza and best supportive care, is deemed sufficient.</p>
6.	<p>The present ICER model fails to adequately capture clinically meaningful improvements and quality of life changes and relies on arbitrary assumptions about long-term efficacy. The proposed model health states are based on binary motor milestone achievements and are not sensitive enough to differentiate between changes in clinical or quality of life improvements that affect QALYs. ICER should alter its methods to allow for more sensitivity in QALY estimates for patients in different SMA health states reflecting 'no milestones,' 'mild milestones,' and 'moderate milestones.' For the long-term model, the base case analysis assumes that motor milestones achieved at the end of follow-up in clinical trials are sustained until death. This assumption is biased, as it conflicts with the trend of continuous improvement observed in patients treated with Spinraza and confers a durability of efficacy to investigational AVXS-101 that has yet to be proven.</p>	<p>The base-case analysis now includes utility benefit in the treatment arms for achieving interim milestones rather than being a scenario analysis. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details. Strong evidence of continued improvement has not been presented.</p>
7.	<p>Motor Milestones Achieved on Spinraza, Page 58: The estimated proportion of 'sitting' patients at different time points was based only on participants in SHINE who attended those study visits. Because the ENDEAR study was terminated early due to the favorable benefit/risk profile established at the interim analysis, not all patients were followed long enough to make it to latter study visit</p>	<p>We have used an alternative method to calculate the short term data for Spinraza (please see Appendix E2).</p>

#	Comment	Response/Integration
	<p>days in ENDEAR and SHINE. ICER disadvantages Spinraza in the multi-stage calculation process as shown in Table E2 and underestimates the proportion of patients in the 'sitting' health state by incorrectly using the number of patients at baseline as the denominator instead of the number of patients at the study visit (e.g. Day 698). ICER's current approach does not produce an accurate estimate of patients achieving the ability to sit in the SHINE study.</p>	
8.	<p>Long-term Assumptions, Page 61: ICER's assumptions on QALY weights for different health states inadvertently apply a downward bias in the value of Spinraza while also overstating the value of investigational AVXS-101. In ICER's current assessment, the 'not sitting' health state assumes the same overall survival of the ENDEAR sham control arm which recognized no treatment benefit. The 'walking' health state is also assumed to have the same overall survival of the US general population. Since a higher proportion of patients were in the 'walking' health state for the investigational AVXS-101 model, these optimistic assumptions were applied to benefit the incremental QALYs and cost-effectiveness ratio of investigational AVXS-101.</p>	<p>We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."</p>
9.	<p>Time Horizon of Long-Term Model, Page 55: ICER mentioned that the extrapolation of motor function milestones was conducted for the long-term model over a lifetime horizon. However, ICER excluded the exact number of years (e.g. 10 years, 20 years, etc.) that was defined as the lifetime horizon.</p>	<p>The time horizon used in the model was 110 years.</p>
10.	<p>Patient Utility Values, Page 64: The patient utility values for the different health states are key drivers of uncertainty and drastically impact the incremental QALY results. Patient utilities have the largest impact on cost-effectiveness results, especially for the later-onset model. ICER decided to use patient utility values from multiple references versus one study. ICER did not discuss or evaluate the key utility data (for Type I and II) from the Lloyd vignette study in its sensitivity analyses. Of the 3 available utility sources, the ERG preferred the vignette study according to the NICE committee papers August 2018.</p>	<p>In the original Biogen submission to NICE the ERG considered that the company's utility values had poor face validity. Alternative utilities from Bastida and Lloyd still have limited face validity. Although none of the datasets were ideal, of the three available utility sources the ERG preferred Lloyd (taken from the slides shown in public).</p> <p>There are two things to note on this: 1) The ERG is choosing between three options and are stating the one with the least lack of face validity, and 2) In the model submitted by Biogen (see page 120 of the first ERG report) in the long-term patients who were alive were either in the best or worse health state; in this model construct only these health states really matter and Lloyd was reasonable for this.</p> <p>Page 134 from the ERG report states, "Overall, the ERG considers that none of the sources are ideal,</p>

#	Comment	Response/Integration
		<p>but prefers the vignette study [Lloyd] as this broadly aligns with the final models' health states and is based on EQ-5D assessments of clinical experts in SMA. The ERG also notes that owing to the company's extrapolation assumptions regarding no deterioration in motor function for nusinersen-treated patients and no motor function improvement for patients receiving usual care, the utility values for the best and worst states have the greatest influence on the ICER in both the early and later onset models."</p> <p>When a different model was used (as described publicly in the second NICE appraisal committee) the intermediate steps were more important, which mean that the lack of face validity of Lloyd was more influential. In personal communication, the ERG for the NICE appraisal has stated that they are comfortable that the utilities used in the ICER report have more face validity than Lloyd and should be preferred.</p>
11.	<p>Treatment Costs, Page 65: Since investigational AVXS-101 is not yet approved by the FDA, its final market price is not yet available and remains highly uncertain. Many long-term costs of investigational AVXS-101 are unknown and sensitivity analyses should be conducted to understand the potential impact of downstream costs on treatment value. There is also large uncertainty regarding the long-term durability and safety of investigational AVXS-101. As there are limited data for investigational AVXS-101 with only 15 patients total, of which 7 have been reported to receive Spinraza post CL-101 trial, total treatment costs should consider inclusion of Spinraza as reported in the real-world.</p>	<p>We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."</p>
12.	<p>As suggested by ISPOR and NICE guidelines, robust methodologies include performing extensive sensitivity and scenario analyses to explore the impact of structural and input parameter uncertainty.</p>	<p>We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."</p>
13.	<p>Later-onset (Types II/III): Page 42-43: It is a failure and limitation of the ICER economic model to not capture any of the benefits of Spinraza versus SOC, as demonstrated in the CHERISH study, and acknowledged in ICER's own clinical assessment for later-onset SMA. These include a significant treatment difference of 5.9 points in total HFMSE score at 15 months in the interim analysis, and a clinically meaningful increase in RULM score from baseline to 15 months (4.2 vs. 0.5) for patients treated with Spinraza vs. SOC. These outcomes should be included in the ICER model as these assessments measure motor ability across</p>	<p>We have now included the utility benefit for achieving interim milestones in the base case analysis.</p>

#	Comment	Response/Integration
	domains that are meaningful to patients and important for activities of daily living. The current ICER model is incomplete without including these outcomes.	
14.	Later-onset (Types II/III): Page 88: As mentioned by ICER and recognized by a key HTA body, the Type II/III model submitted by Biogen to NICE resulted in an incremental QALY difference for later-onset SMA: 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case.	We note that the NICE committee that appraised Spinraza stated that several model assumptions used in deriving these results were overly optimistic, and have added language describing these considerations to the report section on comparisons to other economic models.
15.	Pre-symptomatic: Patients with genetically diagnosed pre-symptomatic SMA (most likely to develop Type I/II) have been studied in the ongoing Phase II, open-label, multi-center NURTURE trial. The study has been presented at three different sources/conference proceedings. Presymptomatic patients treated with Spinraza who were most likely to develop SMA Type I/II (median follow-up = 27.1 months) demonstrated unprecedented outcomes in the context of SMA natural history on event-free survival, motor function, and motor milestone endpoints. NURTURE, a Phase II, open-label, multi-center trial of N=25 pre-symptomatic infants, was determined as a "B+", a lower rating than open-label CL-101 for investigational AVXS-101.	We rated the evidence as B+ because trial results have not yet been published in a peer-reviewed journal.
16.	<p>6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients.</p> <ul style="list-style-type: none"> • Spinraza is used to treat over 6,000 patients worldwide and has become the foundation of care for individuals with SMA. Individuals with SMA live with an uncertain future and are among society's most vulnerable patients. Denying access to treatment can be life-threatening to patients. • Spinraza has been approved for use in over 40 markets worldwide as of January 2019. The clinical benefit of Spinraza has been rigorously evaluated and validated by numerous other HTA bodies. (Germany: First orphan drug ever with major added benefit & third product with major added benefit since AMNOG exists, out of 246 assessments. France: One of the few rare drugs to be recognized as bringing a high level of medical innovation, receiving an ASMR III for Type I and Type II.) • Economic modeling in rare disease is often challenging and frequently does not portray the full picture of the unmet medical needs of the community or adequately address how to objectively assign monetary value to quality of life. Many orphan medicines are not deemed cost-effective (determined by cost per quality of adjusted life year) based on standard accepted cost-effective thresholds. However, many key HTA markets (Germany, 	We are unsure in what way the report contrasts with other HTA assessments and fails to capture the real-world experience of SMA patients. As noted, Spinraza was rated as providing substantial benefits compared with prior standard of care. We agree with the bullet points.

#	Comment	Response/Integration
	France, Australia, Sweden, Scotland, Canada/INESS) recognize Spinraza's value and have ensured access driven by clinical benefit and the robustness of the clinical data.	
Genentech		
1.	<p>Infantile-Onset Model:</p> <ul style="list-style-type: none"> The current model is based on permanent ventilation, death, and motor milestone achievement. Unless 'sitting' or 'walking' were achieved, the utility and health-state cost are assumed to be the same. Given the majority of patients in the ENDEAR trial did not achieve 'sitting' or 'walking,' this model construct essentially ignores the benefits of delayed or circumvented permanent ventilation on patient and caregiver QoL. Literature has showed that patients requiring ventilation had a lower utility score than patients who did not, despite not achieving any motor milestones. In the base case of infantile-onset model, improvements in bulbar function and minor motor function improvements (e.g., head control, rolling, crawling, and standing) are not reflected. In clinical trials, an increase of ≥ 4 points in the CHOP-INTEND score is considered clinically meaningful and this was achieved by a large majority of treated patients in the ENDEAR and START trials. Even when the 'sitting' or 'walking' milestone is not reached, improvements in other motor abilities (e.g., head control and rolling), bulbar function (e.g., eating and speaking) and activities of daily living (e.g., moving and dressing) are clinically meaningful and are associated with QoL improvements for both patients and caregivers. <p>Genentech encourages ICER to adjust the health state cost and utility value in the base case model. Applying different assumptions for permanent ventilation and 'not sitting' will reflect the lower level of support required as well as the improved QoL for patients not requiring permanent ventilation. To the extent possible, ICER should also apply additional utility benefit for improved bulbar function, achieving interim milestones (e.g., head control, rolling), and other functional improvements due to treatment.</p>	The base-case analyses now include utility benefit in the treatment arms for achieving interim milestones rather than being a scenario analysis. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details.
2.	<p>Later-Onset model:</p> <ul style="list-style-type: none"> The model structure includes only three motor milestones: 'not sitting,' 'sitting,' and 'walking.' Although these milestones are convenient for linking to available data on health state utilities, these were not the primary endpoints in clinical trials. For example, none of the treated patients in the CHERISH trial achieved walking without assistance. However, an increase of ≥ 3 points in HFMSE is considered clinically meaningful and this was achieved in 57% of treated patients in the CHERISH trial. 	We have now included the utility benefit for achieving interim milestones in the base-case analysis rather than as a scenario analyses.

#	Comment	Response/Integration
	<p>Such improvements would translate into improved functional ability and QoL, thus should be captured in the model. In addition, the ICER report concludes that Spinraza (nusinersen) is dominated by best supportive care, with higher costs but no improvement in quality-adjusted life years (QALYs) or life years (LYs). This model result lacks clinical validity. Natural history suggests that as SMA progresses, patients lose motor functions and their ability to remain independent decreases over time.</p> <ul style="list-style-type: none"> • Even in the absence of stark improvement in motor milestones such as 'walking,' disease stabilization or prevention of further deterioration are important improvements. A qualitative study demonstrated avoiding declines in function are important for patients and even small changes make a substantial difference for patients to function and thrive. As noted by a clinician in the study, "the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized vehicle or not, and that can make a huge impact on their quality of life and on their ability to be independent." • Additionally, the mean age of patients with later-onset SMA in the economic model was assumed to be 2 years. While this mean age was based on the CHERISH trial population, it is not representative of the population in the real world. The Cure SMA membership database may be a better source for the age used in the model. <p>Genentech encourages ICER to explore an alternative model structure for later-onset SMA. The health states should be defined by patient functional levels that are meaningful to patients and caregivers (e.g., level of independence) and reflect the benefit of treatment. In addition, we also recommend revising the mean age of later-onset patients in this model to be more in line with the real-world population.</p>	
3.	<p>While it takes time for the long-term effects for any new therapy to emerge, the optimistic assumptions around the durability of effect have created bias in favor of Zolgensma (onasemnogene abeparvovec). This is likely due to the one-time administration frequency and the large magnitude of effect observed in a Phase I, single-arm study with a highly selected patient population (N=15). There are multiple key assumptions built into ICER's base case evaluation, given the "unknown duration of expression of the gene therapy." Most notably, ICER assumed motor function milestones achieved at the end of the trial period are sustained until death. Additionally, it was assumed that Type I patients who achieved 'sitting' or 'walking' had</p>	<p>These comments have been noted. A scenario analysis has been performed which restricted the time horizon to 10 years. There is considerable debate regarding the motive for the use of Spinraza after Zolgensma resulting in the base-case assuming that 50% of those who received Spinraza would have declined a milestone otherwise.</p>

#	Comment	Response/Integration
	mortality similar to Type II and Type III patients, respectively. However, despite motor milestone improvements, 5 out of 12 (42%) patients in the START trial (cohort 2) still required ventilation, an intervention not common for Type II or Type III patients. Moreover, 5 out of 12 patients treated with Zolgensma also went on to receive Spinraza after the end of the study period indicating a need for additional therapy in some patients.	
4.	In ICER's model, key drivers of uncertainty are (1) monthly cost, (2) utility values for 'sitting,' 'non-sitting,' and 'walking,' and (3) the length of survival associated with the 'sitting' and 'walking' health states for infantile-onset patients. Of note, none of these estimates are from clinical trials or robust observational studies. In many cases, proxy estimates and assumptions were used. These may have led to a low level of precision in parameter estimates, leading to further uncertainties surrounding model results.	We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."
5.	Lastly, cost and disutility of treatment-related adverse events should be captured in the model as those events are well characterized and distinct from disease-related complications. Similarly, cost and disutility associated with intrathecal administration should be accounted for. Specifically, facility costs associated with intrathecal administration, in both inpatient and outpatient settings, should be included.	The costs of administration are described in detail in Table 4.8 in the section "Administration and Monitoring Costs." As explained in the draft evidence report, given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
6.	The short-term and long-term model results would be more meaningful, if presented separately. For the long-term model, it would be more conservative to adopt a 5-year or 10-year model horizon as the base case rather than lifetime horizon. A shorter time horizon would also be in line with ICER's last evaluation of a gene therapy (Luxturna™ [voretigene neparvovec-rzyl]) which applied a 10-year model horizon as the base case. Additionally, the lack of nationalized healthcare in the US makes the shorter-term horizon more relevant in payer decision making.	We have now included a scenario analysis using a shorter time horizon of 10 years.
7.	Revise the base case to assume a proportion of Zolgensma patients lose motor function over time based on the fact that ~40% of patients from the START trial subsequently received Spinraza.	The base case analyses already assumes that 50% of the Zolgensma patients who receive Spinraza lose motor function milestones at the end of the short-term model. Scenario analyses were performed assuming a greater proportion lose their milestones at the end of the short term model (please see Table 4.22).
8.	Vary utility and cost parameter values by 20% instead of 10% in sensitivity analysis given the high level of uncertainty in the model.	We have now varied the parameter values by 20% in the sensitivity analyses.

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9.	Include the cost and disutility related to adverse events and the facility cost and disutility associated with intrathecal administration in the model.	The costs of administration are described in detail in Table 4.8 in the section "Administration and Monitoring Costs." As explained in the draft evidence report, given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
10.	We believe that caregiver burden should be included in any cost-effectiveness analysis determining societal value. The impact of SMA on caregiver productivity and QoL is well documented in published literature. In this draft report, caregiver burden is excluded because ICER believes its inclusion may "lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer." However, in a cost-effectiveness assessment of pediatric interventions, incremental cost-effectiveness ratios on average decreased by 31% when family spillover effect was included. Genentech strongly recommends that ICER include caregiver burden by including productivity and QoL impact in the infantile-onset, later-onset, and pre-symptomatic models.	There are a considerable number of issues around including spillover utility effects that do not yet have consensus around methodology. Some of the key issues being the number of caregivers to account for, differentiating family effect from caregiver effect, accounting for relationship dynamics over time between patient and caregivers that affect health care decision making, and subsequently the patient and caregiver utility, and the trajectory of caregiver utility post-milestone outcomes such as death. We reviewed the literature to identify pertinent caregiver utilities in this population but found none that we deemed satisfactory to use. We are happy to consider any studies measuring caregiver utility for this population, for our analysis.
Clinicians and Health Economists		
Richard Finkel, MD		
1.	This detailed analysis relies on many assumptions and a very small sample size with limited duration of observation under treatment. The conclusions made in this report are fraught with uncertainty. While the goal of this ICER evidence report is certainly of high merit, it is premature to endorse the conclusions drawn by the authors. Later analysis of a larger sample of treated patients who are observed over a longer period of time will be of greater value.	We agree that there is a substantial degree of uncertainty in many of the report's conclusions, and have highlighted these areas in the report. However, these therapies are either already approved or nearing an FDA decision and despite the uncertainty present in the evidence base, patients and clinicians will need to make decisions about how to use these therapies, and payers will need to develop coverage policies. We believe ICER's independent analyses to be an important source of information that can inform these decisions.
Louis Garrison, PhD		
1.	With regard to this SMA report, these arguments would suggest that ICER is being too conservative in applying a cost-per-QALY threshold of \$150,000 per QALY in projecting a "value-based price" (VBP) for onasemnogene abeparvovec. ICER does recognize a broader range for rare diseases of up to \$500,000 per QALY, and should consider, in this instance, either not making a specific projection for a VBP based on \$150,000 per QALY, or presenting it at a	While our threshold prices extend to the \$500,000 per QALY threshold for reviews conducted under ICER's ultra-rare disease framework, our value-based price benchmarks are still the prices that would meet the \$100,000 to \$150,000 per QALY threshold. Regarding our modified societal perspective, we have not included the family spillover utility affect in our analysis. While we

#	Comment	Response/Integration
	<p>higher level or as a range with a higher upper bound. Given that onasemnogene abeparvovec has not been launched, the device of using “placeholder price” of \$2,000,000 is understandable. However, it may create misleading benchmark: for example, the US Government values lives at closer to \$10 million (https://www.transportation.gov/regulations/economic-values-used-in-analysis).</p> <p>Furthermore, given the grave, negative implications of having a child with SMA Type 1 for parents and caregivers, ICER should emphasize the societal perspective. It was not clear to me whether the “Modified Societal Perspective” alternative in the report captures the “family spillover” effect, e.g., on the (dis-)utility of parents and caregivers. Of course, as outlined in our ISPOR report, augmenting cost-effectiveness analysis—beyond the cost-per-QALY—affects the calculation and/or interpretation of the appropriate CET.</p>	<p>recognize capturing its effect in SMA, we have outlined reasons for not including it in the appendix of our report.</p>
Patient Advocacy Groups		
Cure SMA		
1.	<p>Within the report are multiple errors showing a lack of basic understanding of the disease. For instance, the report states that “there remains considerable uncertainty in the generalizability of the results” (page 48). However, Spinraza clinical trials were completed in patients with SMA types I-III. SMA types I-III represents approximately 95% of patients with SMA. Due to the genetic homogeneity of SMA, the mechanism of action for Spinraza and Zolgensma is the same across the disease spectrum.</p>	<p>While SMA is attributed to a specific gene, there is a spectrum of response to treatment that has been observed across patients in the trials.</p>
2.	<p>Additionally, this report does not seem to understand the basic biology of SMA stating on page 27 that “Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arm. The direction of potential bias in results is unclear as the patients receiving Spinraza may be at higher risk of death and other complications but may also have a greater potential to improve.” The progressive loss of motor function is due to loss of motor neuron innervation. An important consideration for therapeutic efficacy is that motor neurons cannot be restored after being lost and this limits the time window allowing for maximal improvement.</p>	<p>We have updated the text to address your concern.</p>
3.	<p>The long-term extrapolation model for non-sitters is flawed. The long-term model utilizes a lower mean survival of 1.55 years for non-sitters compared to a mean survival of 5.3 years for permanent ventilation thus assuming significantly poorer survival for non-sitters compared to permanent ventilation, even though the non-sitter group</p>	<p>The base case analyses now assumes that the survival of patients on Spinraza is independent of permanent ventilation, however, the survival for patients not receiving permanent ventilation on best supportive care has remained the same. Furthermore, there is also utility benefit in the</p>

#	Comment	Response/Integration
	has showed better outcomes and improvements following treatment with Spinraza. The ENDEAR trial demonstrated a 47% reduction in the risk of death or permanent ventilation in the Spinraza treated group compared to control (Finkel et al, NEJM, 2017). The life years for the SMA type I not sitting Spinraza treated model is severely underestimated.	treatment arms for achieving interim milestones. Please see Table 4.2 for more details.
4.	Throughout the report, clinical trial data is misinterpreted in the ICER models, which has a major impact on the determination of cost effectiveness of the therapies under evaluation. Table 3.4 of the report correctly indicates that maximally 29% of patients had the ability to sit independently towards the end of the SHINE extension study (Castro et al, NMD, 2018). However, in section 4 of the report a value of only 11% is used. This lower value appears to be calculated using the total number of patients receiving Spinraza in the ENDEAR trial (n=81, Finkel et al, NEJM, 2017), rather than the number of patients being assessed at that particular time point (n=31, Castro et al, NMD, 2018). By doing so, the model unfairly assumes unfavorable outcomes for the unassessed 50 patients, i.e., none would have sat if assessed. Meanwhile, the actual reason that many in the full cohort were not assessed at this time or beyond is that they had not yet reached this point in the study (meaning that they had been on drug less time than the actual timepoint under evaluation).	We have used an alternative method to calculate the short term data for Spinraza (please see Appendix E2).
5.	Furthermore, there are major flaws in framing the outcomes of pre-symptomatic treatment with Spinraza, which downplay the dramatic impact on survival and function in this situation compared to natural history. Trial data demonstrate that most infants treated proactively, when free of symptoms, achieve the motor milestones of walking and standing. In fact, 22 of 25 were able to walk with assistance and 17 of 25 were able to walk independently (Swoboda et al, WMS, 2018). To date, no pre-symptomatic SMA infant treated with Spinraza in this study has died or required permanent ventilator support. The assessment of pre-symptomatic treatment benefit is wrongly framed by a comparison to the development of healthy children. Natural history outcomes regarding individuals with the same SMN2 copy number should be used for comparison, not outcomes in unaffected children.	In Table 3.11, we include the 1st-99th percentiles of the windows of WHO milestones. These percentiles are also included in the manufacturer's presentation of results. See e.g., De Vivo's presentation of interim NURTURE results presented at the 2018 Cure SMA Annual Research Meeting (slide 8).
6.	Finally, as with any treatment whose approval is based on clinical trials of a feasible and ethical duration, there is always ongoing uncertainty about longer-term outcomes. However, the report has a lengthy section (3.4) about clinical trial controversies that seems unwarranted. These would be better framed as important issues that would ideally now be examined using real world data capture on drug efficacy and safety. We believe ICER should frame	Thank you for raising this concern. We have added text in Section 3.4 to note the potential for Zolgensma to provide a life-long benefit. We believe that the base case scenario has been "optimistic" where choices were made, which is reflected in the larger number of "conservative" scenarios.

#	Comment	Response/Integration
	<p>long-term uncertainties in a more balanced manner, leaving open the possibilities of both pessimistic and optimistic scenarios for future results. Currently, for example in tables 4.21 and 4.22, there are only 2 and 3 positive scenarios modeled out of the total in each table.</p>	
7.	<p>ICER assigns benefit to the patient only if the drug allows for obtaining milestones such as sitting or walking. Meanwhile patients have reported, and the FDA has recognized, the great value in abilities that allow for more independence and activities of daily living (McGraw et al, BMC Neurol, 2017; and Rouault F et al, NMD, 2017). For some patients and their families, simply not getting worse is an improvement and a meaningful outcome. It should also be noted that even incremental increases in a patient's motor abilities may alleviate the stresses and challenges involved in caregiving by allowing patients greater ability for self-care. These meaningful and valued milestones are not factored into this analysis; however, the complete set of clinical trial data from the early open label studies to the pivotal ones demonstrates these improvements in SMA type I, II, and III participants.</p>	<p>The base-case analysis now include utility benefit in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details.</p>
8.	<p>We know that most patients show clinically meaningful improvement with Spinraza, yet ICER ignores these when constructing this analysis. This lack of patient perspective about the value of these milestones and incremental improvements seriously weakens ICER's models, and therefore, the analysis of value and efficacy is incomplete. It is a disservice to all with SMA that a report which could impact access to life saving treatments for some of the most vulnerable members of society does not include their perspective.</p> <p>The ICER models show that only 1% of SMA patients gain any meaningful benefit from Spinraza. This ignores and contrasts with:</p> <ul style="list-style-type: none"> • 51%, vs 0% untreated, HINE Responders. • 45%, vs 0% untreated, with Head Control. • 71%, vs 3% untreated, CHOP Responders. • 57%, vs 26% untreated, HFMSE Responders. <p>The process of determining QALYs for patients permanently on ventilators and those who are non-sitters appears arbitrary and does not take into account the wide range of patient outcomes in between these two statuses. The analysis also fails to take into account the advances in technology that have made it possible for physically limited individuals to meaningfully contribute to society in ways never before possible. Many patients who have not</p>	<p>The base case analysis now include utility benefits in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms but not for best supportive care. Please see Table 4.2 for more details. We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."</p>

#	Comment	Response/Integration
	achieved the arbitrary ICER chosen milestones are productively employed.	
9.	Moreover, incorrect assumption and subsequent erroneous modeling occurred around the fact that some subjects who received Zolgensma in the START trial were subsequently treated with Spinraza. The assumption that Spinraza was added after Zolgensma due to a deteriorating health status led to modeling that “half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth (33% * 50%) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period.” There is no evidence to support this assumption. The more likely explanation is that families’ expectations are high for best outcomes and families will do everything possible to get their child every available treatment in order to eliminate as many symptoms as possible.	Our clinical expert suggested thought that both rationales for seeking Spinraza therapy were plausible (i.e., patients seeing benefit would want to achieve additional benefit and patients at risk of losing milestones would want the other therapy to prevent further loss). As such, we assumed that half of the patients would lose a milestone.
10.	For a pediatric and typically fatal disease such as SMA, now with transformative and impactful treatments, the ICER model of financially discounting life years has a significant effect. The controversial approach of using a financial model for discounting life years (prior to any utility discounting) should be clearly disclosed and have scenario analyses to indicate the impact on any conclusions.	Discounting costs and outcomes in health economic modeling is standard practice. We have now included undiscounted costs and outcomes of our base case analysis in the appendix of the report.
Muscular Dystrophy Association		
1.	With regard to the value of treatments for SMA as set out in the draft report, we would note that the evaluation of milestones may not fully reflect the experiences and needs of the patient community. For example, gains in mobility, such as the ability to sit or to reposition unassisted, can represent significant, positive change in the life of an individual living with SMA and their caregivers. Improvements in mobility, however small they may be deemed, often represent major improvements in quality of life and the value of these gains cannot be discounted. In addition to health improvements that may be associated with increased mobility, increases in mobility are directly related to independence, which is a critical factor for those living with neuromuscular disease. Similarly, respiratory function is also major concern for the SMA community. The significance of what one may consider even relatively small gains for SMA patients in this area must be reflected in any evaluation. Further, with SMA being classified as not only a rare disease, but as an ultra rare disease with a significant burden, the QALY applied in the report is likely insufficient. This is important as such determinations may impact access to treatment. Additionally, while the report	The base-case analyses now include utility benefits in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the “not sitting” health state of treatment arms. Please see Table 4.2 for more details.

#	Comment	Response/Integration
	notes that there are “common limitations” in applying the framework in rare diseases, there are further limitations in the draft report as Zolgensma has not yet received FDA approval. Thus, for example, it does not yet have a price. Similarly, and as noted in the report, there are no coverage policies associated with Zolgensma to evaluate.	
Patients Rising Now		
1.	As we’ve previously stated, “evaluating the clinical and market potential of medicines prior to approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult.” In the Draft Report ICER has taken an additional leap to include a completely fictional construct. Therefore, we think it would be analytically and socially responsible for ICER to reissue an updated Draft Evidence Report that includes actual data for Zolgensma after FDA approval when its labelled indications and warning will be known, as well as the list price – and of course separately publish any fictional constructs of potential medicines in more appropriate publications.	<p>Policymakers need to make decisions about appropriate pricing, coverage, and clinical use at the time a treatment is approved by the FDA despite the challenges in doing so, and our reports serve as an independent assessment that can inform these decisions. ICER has an established update process for revisiting reports when important new evidence emerges.</p> <p>We have also added additional language to the report describing the policy considerations the “Drug X” analysis is intended to inform.</p>
2.	While the genetic cause of SMA is known, and tests for determining a patient’s status are available, we share ICER’s concern about the limited data available about Spinraza and Zolgensma. However, models or projections based on uncertain data is inherently an error prone process and a fundamental flaw in this Draft Report, as well as many other ICER activities. The 189-page Draft Report contains numerous references to this uncertainty, including the admission on page 183 that “the true uncertainty is likely to be more than that represented in our probabilistic analyses.” Nevertheless, the Draft Report makes economic declarations that it clearly recognizes others will rely upon for decisions affecting patients and families.	Therapies such as Spinraza and Zolgensma may produce substantial long-term benefit, but at non-negligible costs to patients and the health system. Economic models such as ours serve to aid the decision-making process when choosing the right treatment for patients, especially in the absence of long-term data on their benefits. This absence of long-term data poses uncertainty regarding health and economic impacts of such treatments, which is why we include sensitivity and scenario analyses in an attempt to address these uncertainties.
3.	<p>We also appreciate the complications of modeling based upon clinical trials that are single armed or limited in duration. However, for certain innovations, single arm trials are the appropriate structure and research methodology. As has been written, “Such comparisons [in a single arm study to the natural history of the disease] are meaningful only when the expected outcomes in the absence of the intervention are well-known, and the expected effect size from the intervention is large,” which clearly is the situation with Zolgensma.</p> <p>Similarly, projecting long-term outcomes from trials of limited duration is a well-recognized issue in clinical research. However, this issue has largely been settled, since waiting for lifetime results (i.e., 60+ year trials) is impractical, would deny patients access to treatment that have demonstrated short or intermediate term benefits,</p>	<p>ICER’s evidence rating for Zolgensma follows the rationale described here, and additional context regarding these ratings can be found in earlier responses.</p> <p>As noted in other responses, clinicians, patients, and payers must make decisions about how to use and cover these therapies at the time of their approval, regardless of the maturity of the evidence base. It is also important to note that drugmakers select the prices of their therapies despite these uncertainties. We also note that despite these uncertainties, both therapies have received highly favorable evidence ratings.</p>

#	Comment	Response/Integration
	<p>and would also effectively terminate any investments in such research.</p> <p>Overall, the objections ICER raises about the sparsity of data are due to the self-determined timing of ICER's activities (i.e., before or shortly after FDA approvals) rather than the realities of the data itself. This is akin to a paraphrase of the Heisenberg Uncertainty Principle, i.e., the sooner you get the data, the more uncertainty there will be, and conversely the more you demand certainty of data the longer you will have to wait - and more people and society will be denied the benefits of the resulting innovations. Thus, while families and patients with SMA would clearly benefit from better treatment options, we believe that ICER's Draft Report – both its technical aspects and overall approach – are counterproductive to that goal.</p>	
4.	<p>ICER's assumption filled process fundamentally risks incorrectly modeling the real world. For example, it is widely recognized that modeling of uptake and usage of new medicines can be very far off from what actually occurs once a treatment is approved by the FDA. This was evident from the actual usage of the first new medicines to treat hepatitis C (which had initial usage much greater than had been projected), and those to treat very high cholesterol because of PCSK9 protein variants (which had initial usage that was much less than projected). What is also interesting in both those cases was that over time, there was dramatic decline in the net prices paid by payers, although what patients paid may not have fallen to the same extent – which is of course an ongoing concern – and a factor ICER also does not address in its framework process.</p> <p>We would appreciate ICER's comments about how its methodology does not account for such real-world market dynamics that effect prices and overall costs to payers, patients, and society.</p>	<p>Real-world evidence on current drug market share is usually data that is confidential and even if shared with ICER, cannot be used in the public domain due to the sensitive nature of the data. As for market uptake, as you rightly state, it can be far off prediction, which is why we use extreme scenarios in our budget impact models, which are intended to serve as "plug-and-play" models for different payers based on the population they cover and their respective budgets.</p>
5.	<p>The Draft Report provides a link to the list the stakeholder from whom ICER requested input, but not those from whom it actually received input. That list should be provided.</p>	<p>This list includes organizations that have provided input as well as those that have been invited to provide input.</p>
6.	<p>The Draft Report only lists one "Expert Reviewer," and that individual appears to have only a few years of experience since finishing her doctorate.</p>	<p>Given that each ICER report is subject to a month-long public comment period, we do not believe this to be a limitation of our report. As can be seen in this document, we receive detailed feedback from stakeholders, and much of this feedback is written or informed by clinical expert input. We also note that the reviewer is an expert in SMA clinical outcomes measures and is also a</p>

#	Comment	Response/Integration
		practicing therapist with highly relevant experience.
7.	The Draft Report states that “Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the SMN2 gene; Humana states that patients may have no more than two copies.” Can you explain the rationale for why different insurers would have such opposite prior authorization criteria? Also, Humana appears to have updated their criteria so that individuals with Delayed Onset SMA can have “no more than three copies of SMN2.”	This section is intended to describe how various payers cover the therapies of interest for a given review and does not address the rationale behind these decisions. Because we did not develop these policies, we cannot comment on the reasons why each payer chose such a policy. We expect to discuss these considerations during the policy roundtable at the upcoming public meeting.
8.	It seems the 100% survival rate for Zolgensma has now been reported at 24 months.	Thank you for your comment. We have added the longer-term follow-up data for Zolgensma.



Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Thursday • March 7, 2019 • 9:30 am to 4:00 pm

Alcott Ballroom, Omni Parker House, 60 School Street, Boston, MA 02108

Time	Activity
9:00 am—9:30 am	Registration for Public Attendees
9:30 am—9:45 am	Meeting Convened and Opening Remarks Steve Pearson, MD, MSc, President, ICER
9:45 am—10:45 am	Presentation of the Evidence Alexandra Ellis, PhD, MSc, AM, Senior Scientist, ICER Matt Stevenson, PhD, BSc, Professor, University of Sheffield
10:45 am—11:00 am	Manufacturer Comments and Discussion
11:00 am—11:30 am	Public Comments and Discussion
11:30 am—12:30 pm	Lunch
12:30 pm—2:00 pm	New England CEPAC Vote on Clinical Effectiveness and Value
2:00 pm—2:15 pm	Break
2:15 pm—3:30 pm	Policy Roundtable
3:30 pm—4:00 pm	Reflections from New England CEPAC
4:00 pm	Meeting Adjourned

January 31, 2019

AveXis, a Novartis company, appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) draft evidence report of treatments for spinal muscular atrophy (SMA). We thank ICER for delivering a complex model and thorough analysis in such a short time. We found the model used appropriate health states that accurately capture the clinical progression of SMA Type 1; including a separate permanent ventilation health state was especially important given the implications for patients. Using a short-term and long-term approach effectively captured the key data available. We agree with the survival data used to model transitions, and for those patients who achieve sitting and walking milestones, using SMA Type 2 and SMA Type 3 data, respectively, was a reasonable approach. Similarly, avoiding the transition from sitting or walking to permanent ventilation was a valid assumption and supported by clinical experts. In addition, the use of a mixed approach for utilities is pragmatic given a lack of disease-specific utilities, and the cost data adequately captures the health state burdens. Finally, the well-thought-out sensitivity and scenarios analyses highlighted key data gaps and provided additional value for decision making.

Detailed Comments and Recommendations

We appreciate ICER's evaluation and willingness to engage stakeholders during the review process. In our review, we identified some methods that we recommend be reconsidered, specifically:

1. We disagree with ICER's base case model assumption that 1/6 of sitting ZOLGENSMA patients return to the not-sitting state at the end of the short-term model, and with ICER's assumption that these patients "required" Spinraza. This assumption is not grounded in evidence and is inconsistent with those made for Spinraza. We acknowledge scenario analysis #6 reports results assuming no loss of milestones, and removing this assumption lowers the ICER by \$17,000 to \$230,000 per QALY for ZOLGENSMA vs BSC. However, we request the modeling team remove this loss of sitting milestones assumption for ZOLGENSMA in the base case. We also request the removal of the word "required" when referencing patients who did receive Spinraza after ZOLGENSMA as there is no evidence to support this language.
 - There is no clinical evidence to support the milestone loss. Importantly, no patients who received the therapeutic dose in the ZOLGENSMA CL-101 24-month study, or the long-term study (maximum follow-up of 30 months) experienced any loss of milestones or worsening disease.^{1,2}
 - There is no evidence that Spinraza was "required" or beneficial for ZOLGENSMA patients in the trial. It is highly implausible that any ZOLGENSMA-treated patient would receive additional benefits by commencing chronic treatment with Spinraza.

ZOLGENSMA is a gene replacement technology based on Adeno Associated Virus (AAV) Serotype 9 as vectors, which has demonstrated long-term gene expression in several pre-clinical and clinical trials. ZOLGENSMA was designed for rapid onset and long-term gene expression utilizing self-complementary DNA technology for rapid gene expression as well as a modified Chicken B-Actin promoter for high-level, robust expression in a wide variety of cell types including motor neurons. Preclinical data support the expectation of long-term gene expression following administration of ZOLGENSMA. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared to control-treated animals who did not survive past

22 days; this suggests continued expressions.³ Gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression. In non-human primates, quantitative RT-PCR was used to demonstrate gene therapy vector-derived mRNA 6 months post-injection, indicating persistence of expression.

The addition of an SMN-enhancing agent more than two years after treatment with ZOLGENSMA lacks therapeutic rationale and biologic plausibility. Swoboda *et al.* demonstrated a precipitous decline in viable motor units over the first few months of life amongst infants with SMA Type 1.⁴ For patients with SMA Type 1, without disease-modifying treatment, over 95% of motor neurons are permanently lost by age one. Following treatment with ZOLGENSMA, a significant majority of motor neurons are expected to take up the vectors and thus express continuously sufficient SMN protein. Motor neurons that fail to take up vectors are effectively untreated and will thus be lost. For this reason, the addition of an SMN2-enhancing agent months to years following ZOLGENSMA dosing lacks biological plausibility – the only motor neurons left, by definition, already express adequate levels of SMN protein. In contrast, there is a plausible mechanism to support administering ZOLGENSMA to patients who have previously received Spinraza (i.e. using Spinraza as a “bridge therapy”). This approach should be regarded as different from a sequential strategy (Spinraza post ZOLGENSMA) modelled in the base case.

- Because there was no evidence of clinical deterioration in the CL-101 trial, it is our contention that the decision to initiate Spinraza post ZOLGENSMA was driven by parental desire, rather than by clinical indication or biological plausibility. It is understandable that parents would have considered additional options, regardless of the lack of scientific evidence to support the plausibility of additional effectiveness (see above). And, while the specific motivations that underlay the decision to initiate use of Spinraza is a private matter between patient’s guardians and physician, these motivations **should not be used** as a foundational assumption that patients were deteriorating or that Spinraza was required. Further, the following points are important:
 1. Among four new milestones reported among participants in the long-term follow-up, three occurred among patients only receiving ZOLGENSMA.
 2. Two of the five subjects who initiated Spinraza discontinued use due to lack of benefit (i.e., no new motor milestones).
- ICER’s approach to ZOLGENSMA milestone persistence, which was modeled as a decline in the absence of evidence, is contradictory to ICER’s approach to Spinraza milestone persistence, which was modeled as consistent despite published data showing a decline in the proportion of sitting patients. Table 4.2 (page 56) of the ICER report states: “In the short-term model for Spinraza, we assumed that the numbers of patients sitting cannot decrease over time”. This is explained in Table E2 and page 158: “The numbers of patients sitting are monotonically increased with time, except for the last time point where the number of patients sitting is lower than the previous time point. It is not clear if this is due to administrative censoring or patients losing milestones. We assumed that this was due to administrative censoring, and in step three, the number of patients sitting at the last time point was set as equal to those in the previous time period.” This assumption’s importance can be observed in the one-way sensitivity analysis for

Spinraza (Figure 4.4, page 72), Scenarios 7a-c for Spinraza vs BSC (Table 4.21, page 75), and where ICER reports 64% of Spinraza QALYs are from the sitting (Table E12, page 168).

- The loss of milestones assumption was not mentioned in the original model analysis plan. Based on the report, it is unclear whether clinical, SMA or gene therapy experts were consulted about this assumption, and a discussion with experts or AveXis may have benefitted this assumption.
 - If the assumption is not removed, for the purposes of balancing the analysis, we request the modeling team conduct a scenario analysis where responders are restored to full health.
2. We request the modeling team conduct a new value-based price (VBP) analysis for the threshold prices in Table 4.26 using the “no milestones lost” assumption for ZOLGENSMA.
 3. As discussed in earlier consultations, we recommend ICER’s “Report at a Glance” should include all relevant thresholds **including** the VBP analysis using a willingness-to-pay of \$500,000 per QALY. This short version report is more accessible for decision makers than long-form reports, and including this figure would be consistent with ICER’s stated objectives for ultra-rare diseases. This request is also supported by a £100K- £300K per QALY threshold for ultra-orphan drugs by NICE.⁵
 4. We find the “ZOLGENSMA vs Spinraza” scenario (Pages 77-8, Tables 3, and 4.23-24) misleading.
 - We recommend this scenario should be removed given the lack of clinical and biologic plausibility for sequential treatment with Spinraza (Point 1), and an unaddressed uncertainty of whether Spinraza would be covered for ZOLGENSMA-treated patients by US insurers.
 - If this scenario is not removed, we request the scenario be relabeled as “ZOLGENSMA *followed by* Spinraza vs Spinraza” for clarity, as this reflects the true comparison.
 - Further, it would be appropriate for ICER to modify the scenario and report the scenario where ZOLGENSMA (monotherapy) is the comparator against the sequential treatment. The current ICER of \$202,000 (Table 4.23, page 78) shows the incremental benefit of ZOLGENSMA as a bridging therapy to Spinraza treatment, an indication for which ZOLGENSMA has not been studied, nor follows clinical rationale. ZOLGENSMA as the comparator shows the incremental benefit of adding Spinraza post-ZOLGENSMA. Based on current values in the reports, we have calculated this ICER for ZOLGENSMA *followed by* Spinraza vs ZOLGENSMA to be \$1,415,323/QALY $((\$5,240,000 - \$3,485,000) / (12.57 - 11.33) = \$1,755,000 / 1.24)$. Adding Spinraza to ZOLGENSMA-treated patients would not be clinically justified nor cost-effective.
 - We also request the modeling team report an additional scenario analysis of “ZOLGENSMA monotherapy (without milestone loss) vs Spinraza monotherapy” so that the committee, and subsequent audiences, can more fully consider the long-term value for money.
 - In the event ZOLGENSMA *followed by* Spinraza vs Spinraza scenario is not removed, based on recent data from the ZOLGENSMA managed access program (MAP) (16 out of 20 =80% MAP patients received Spinraza prior to ZOLGENSMA), we request ICER to conduct a switch strategy scenario (1 to 3 doses of Spinraza *followed by* ZOLGENSMA) and report the ICERs for switch strategy vs BSC and Spinraza monotherapy.
 5. To match current recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine, NICE, and HTA agencies in The Netherlands and Belgium,⁶⁻¹² and given the long-term

health benefits provided by ZOLGENSMA, we request the modeling team conduct additional scenario analyses using differential discounting (i.e., 3% for costs and varying utilities from 0% - 3%). Also, as recommended by the Second Panel,¹² we request that the modeling team include discounting as part of the one-way sensitivity analysis for all treatments.

- There is broad agreement that in cost-effectiveness analysis (CEA), future outcomes should be discounted, and their present values calculated so that cost-effectiveness ratios will be appropriately adjusted for the differential timing of costs and consequences. However, there is disagreement over the appropriate discount rate to use. The Second Panel noted that the appropriate discount rates for costs and health will depend, among other things, on fixed health care budgets, the social objective of maximizing welfare vs health, and social time preferences (which may be different for health vs consumption).¹² The Second Panel recognized the uncertainty around the appropriate discount rates from societal and health care sector perspectives. The Panel noted that “since the goal of the Reference Cases is to promote comparability across studies, we recommend that a 3% interest rate be used for both costs and effectiveness from both the societal and the health care sector perspectives.”¹² We recognize this rate was used in the ICER model. However, the Second Panel stated it is always advisable to perform sensitivity analyses for any baseline discount rates used, especially when the costs and benefits are incurred at different times for different interventions. More recently, others have argued, based on theoretical and empirical evidence, that the Second Panel’s recommended discount rate of 3% per annum is too high, resulting in systematic bias against health technologies with upfront costs and long-term health effects.⁶
 - We note ICER is preparing its framework for curative therapies and hope ICER will consider the merits of differential discounting in its assessment. As the standard practice in the US is to discount benefits at the same rate as costs, the benefit of potentially curative medicines may be severely misrepresented. In the meantime, given the considerable public attention to ICER reports beyond the field of health economics, it would be beneficial to patients and members of the public for an undiscounted survival benefit to be published, as well as a VBP based on undiscounted benefits. This is demonstrated well by an example from the published draft report. Table E10 (page 167) reports a gain of 32.4 undiscounted life years for the ZOLGENSMA cohort. To test the ICER per QALY, we multiplied the corresponding utility value for each health state (using 0.88 as an average for walking) by the undiscounted LYs (by health state) for ZOLGENSMA to yield the undiscounted QALYs. Our calculations show ZOLGENSMA yields 22.4 undiscounted QALYs; in the base case (3% discounting) ZOLGENSMA yields 11.33 QALYs. Removing discounting nearly doubles the QALYs. Using costs from Table 4.13 (page 70) shows the benefit of differential discounting (3% costs, 0% utilities), as the ICER for ZOLGENSMA vs BSC lowers to \$123,000 / QALY from the base case of \$247,000 / QALY.
6. We appreciate HTA bodies outside the US frequently use stopping rules in CEA. We disagree with the base case 24-month stopping rule assumption for Spinraza, as this is not likely to be indicative of US clinical practice. We request that the modeling team report the results from scenario analyses where different Spinraza stopping rules are tested (e.g. 36 months, 48 months).
- Insurance guidelines for Spinraza suggest that Spinraza can be continued if it helps to improve, maintain, or slow the disease progress.¹³ Spinraza is indicated for life-long treatment. Therefore,

even if patients do not achieve a milestone (i.e., not sitting to sitting), it is expected that they would continue treatment. Understanding how the stopping rule affects the Spinraza vs BSC ICER results will be important when assessing long-term value for money.

7. We request the modeling team remove the “Drug X” pre-symptomatic analysis. We enthusiastically agree that there is promise for treating SMA patients early. However, there is little clinical evidence to support these analyses, thus the “Drug X” analyses are premature and speculative. Also, as the results rely heavily on patient mix, they are not generalizable. The patient mix does not match the ongoing pre-symptomatic study AveXis is conducting which means ICER’s results are unlikely to reflect how ZOLGENSMA will be used in practice. Further, it is unclear how SMA patients may be identified pre-symptomatically as not every US state has a compulsory newborn SMA screening program. Therefore, the source and validity of pre-symptomatic prevalence assumptions are unclear.
8. We request optimistic versions of scenarios 7a-7c (i.e., assume 10/20/30% of sitting [or not sitting] patients transition to walking [or sitting] at the end of the short-term model) to test uncertainties.
9. We request the modeling team conduct a scenario analysis accounting for a blended Spinraza price: 60% with \$127,500 (Table 4.7, page 66) and 40% with the hospital markup ranging from 8% to 60%. In Table 4.7, ICER assumes no hospital markups for Spinraza. However, in calculating the total administration cost for Spinraza, ICER assumes 40% of patients receive Spinraza in inpatient settings (Table 4.8, page 5). If 40% of patients receive Spinraza in inpatient settings, it would be reasonable to account for the hospital markup costs for Spinraza. Our range recommendation is from clinical experts who have advised hospital markups could range between 8%-60% per dose.
10. Intubation in the US is more common. We request ICER conduct a scenario using pooled survival curve of non-invasive and tracheostomy patients (PV to death¹⁴) with a survival limit (e.g. 22 years).
11. There are several important considerations for ZOLGENSMA that should be added to Section 5 – Potential Other Benefits and Contextual Considerations. We list these below.
 - ZOLGENSMA is a one-time, one-hour IV treatment that should eliminate patient and caregiver anxiety, inconvenience, and complexity associated with repeated lumbar punctures needed for Spinraza while improving patient outcomes.¹⁵
 - The benefits of ZOLGENSMA extend beyond improved patient survival and quality of life. These children will have the potential to attend school and require substantially reduced levels of care, allowing family to return to work, with subsequent mental health and financial benefits.
 - Due to its mode of action and its one-time dosing, ZOLGENSMA may reduce the existing burden on caregivers by helping to eliminate the need to continuously navigate complex and often-changing health insurance coverage policies.

In summary, we largely agree with ICER’s findings and analysis. This is a challenging disease to model, but the findings are generally in agreement with our expectations. ICER highlights the milestones achieved by ZOLGENSMA patients, who otherwise would have experienced rapidly progressing and lethal disease. We believe that incorporating the important issues highlighted above will further improve the scientific validity and usefulness to audiences of the evaluation.

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10. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. *Pharmacoeconomics*. 2018;36(7):745-758.
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15. La Foresta S, Faraone C, Sframeli M, et al. Intrathecal administration of Nusinersen in type 1 SMA: successful psychological program in a single Italian center. *Neurological Sciences*. 2018;39(11):1961-1964.

January 30, 2019

Dear Dr. Steve Pearson,

Thank you for the opportunity to comment on ICER's SMA Draft Evidence Report. Outlined below are **six** key issues with ICER's assessment that have the potential to significantly affect the results presented to the New England CEPAC. A large amount of research, analysis, and data with significant uncertainties have been distilled into a clinical value assessment and incremental cost-effectiveness ratios for each treatment that will form the basis of New England CEPAC's votes on evidence and value. We strongly encourage ICER to ensure that any presented conclusions fully capture clinically meaningful improvements observed in studies and adequately account for uncertainties and current limitations.

Biogen values credible, reliable scientific and economic evidence that is based on robust and extensive data packages, valid assessment methodologies, and meaningful input from subject matter experts and patient communities. After careful review, Biogen believes that the current ICER report fails to meet these standards. As a result, we believe there are important questions about the validity of the draft assessment and risks to its use in healthcare decision making.

Our primary comments and recommendations are outlined below:

1. The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings.
2. ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101.
3. ICER's assumptions around durability of treatment effects for investigational AVXS-101 do not take into account potential uncertainties associated with gene therapies. ICER's new initiative to develop methods to guide value-based pricing of potential cures highlights the need for a more robust approach.
4. Key assumptions in the draft assessment unduly disadvantage Spinraza, and important areas of uncertainty are not adequately addressed. Incremental cost-effectiveness ratio values are inappropriately presented as absolute numbers instead of ranges or intervals to account for uncertainty.
5. The importance of Spinraza's approval and evidence supporting the ability to treat broad and diverse patient populations is not accurately captured in the ICER assessment.
6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients.

DETAILED COMMENTS AND RECOMMENDATIONS

1. **The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings.**
 - Page 51: The rationale for assigning investigational AVXS-101's uncontrolled, single-site, open-label Phase I CL-101 trial, which enrolled only 12 patients in the proposed therapeutic dose cohort, an evidence rating of an "A" is unsubstantiated. The ranking of CL-101 in infantile-onset SMA eliminates the large difference in evidence between investigational AVXS-101 and the robust Spinraza clinical trial data. As stated by ICER on Page 51: *"Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have **high certainty** that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A)."*
 - According to ICER's evidence rating matrix, an "A" rating requires high certainty in level of evidence and a substantial comparative net benefit effect. In reference to investigational AVXS-101,

we believe that the net health benefit is currently **uncertain**, particularly given **lack of data on the durability of investigational AVXS-101**. The long-term efficacy of investigational AVXS-101 is unknown, with data limited to a single-site, open-label, uncontrolled study of a small population of infants with SMA treated for just over 24 months as of the last report.ⁱ Furthermore, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended.ⁱⁱ

- ENDEAR, a randomized, multi-center, international, double-blind, sham-controlled Phase III study, with a total of 121 participants,ⁱⁱⁱ should not receive the same rating as an uncontrolled trial with only 12 participants. Furthermore, patients with infantile-onset SMA who were treated with Spinraza in ENDEAR have been followed for nearly 3 years in the SHINE extension study, during which additional improvements in motor milestones and general motor function have been observed.^{iv}
- There were two patients (N=2/12 or 17%) in the high dose cohort of CL-101 who were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]).^{iv} This raises questions on the sponsor's ability to select appropriate patients for an SMA Type 1 study and why these two patients were included in the proposed therapeutic cohort.
- Page 25-26: 17 out of 19 publications meeting PICOTS criteria were Spinraza studies, which points to its solid evidence base while also underscoring the prematurity of the ICER analysis of investigational AVXS-101.
- An ICER report from October 2018 assigned a "C+" rating to the evidence for investigational inotersen for hereditary transthyretin amyloidosis (hATTR) based on NEURO-TTR, a Phase III, randomized, controlled trial with 172 total patients followed for over 15 months after treatment. Similarly, in a report from February 2018, ICER assigned a "B+" rating to voretigene neparvovec for biallelic RPE65-mediated retinal disease, based in part on a Phase III randomized control trial (Study 301) with 31 participants. This represents a large inconsistency in ICER evidence ratings across evaluations.

2. ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101.

- Although ICER did not assign an evidence rating comparing investigational AVXS-101 versus Spinraza for infantile-onset SMA in the Comparative Clinical Effectiveness section of its report (Section 3.5), the foundation of ICER's economic modeling in Section 4 is the clinical data, for which ICER makes no adjustments to account for differences in baseline characteristics between study populations, as recommended by ISPOR's Good Research Practices.^v
- Page 51: ICER notes *"Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of investigational AVXS-101 versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I)."*
- Page 31: Key baseline characteristics of ENDEAR and CL-101 indicate that the patient populations have clinically relevant differences, with patients in ENDEAR having a comparatively less favorable profile in terms of potential to respond to therapy:
 - Treatment with Spinraza was initiated later after disease onset compared to investigational AVXS-101: Patients treated with Spinraza in the ENDEAR study (**mean age: ~5.3 months**) were older at study initiation compared to investigational AVXS-101 patients in the high dose cohort of CL-101 (**mean age: ~3.4 months**).
 - Patients treated with Spinraza in the ENDEAR study had a longer disease duration (3.3. months) compared to patients treated with investigational AVXS-101 in the high-dose cohort of CL-101 (approximately 2.0 months).
 - There was a greater proportion of patients treated with nusinersen in the ENDEAR study (26%) who required respiratory intervention at baseline than those in the high-dose cohort of CL-101 (17%),

which could have an important impact on clinical outcomes, such as event-free survival and respiratory outcomes. Table 3.1 incorrectly transposes numbers from those reported in Table 1 of the Mendell et al 2017 publication.^{vi}

- **Page 36:** As noted in the previous point, two patients (N=2/12 or 17%) in the high dose cohort of CL-101 were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]).^{iv} Due to early treatment and higher baseline motor function, these patients may have had more opportunity to respond compared to patients treated with Spinraza in ENDEAR who received initial treatment at a later age and had lower baseline motor function.
- **Page 78:** Of great concern, ICER estimates an incremental cost-effectiveness ratio comparing Spinraza and investigational AVXS-101 in the infantile onset patient population based on a naïve, **unadjusted** comparison of trial data. In contrast, HTA bodies such as NICE in the UK and the TLV in Sweden are cautious to conduct such cost-effectiveness evaluations based on naïve comparisons and ask for adjusted comparisons also in areas where such comparisons are challenging to conduct, as exemplified by their evaluations of CAR-T therapies such as Yescarta and Kymariah.^{vii,viii,ix}

3. ICER's assumptions around durability of treatment effects for investigational AVXS-101 do not take into account potential uncertainties associated with gene therapies. ICER's new initiative^x to develop methods to guide value-based pricing of potential cures highlights the need for a more robust approach.

- Lack of consensus exists on appropriate methods to assess the substantial uncertainty around long-term safety and effectiveness of gene therapies.
- In the absence of a consensus on appropriate methodology, ICER should utilize durability assumptions for its evaluation of investigational AVXS-101. One consideration would be to use what was previously applied for durability assumptions for the gene therapy voretigene neparvovec for inherited retinal disease.^{xi} In this previous assessment, treatment effect was assumed to be maintained for 10 years, followed by a 10-year waning of effect, after which the rate of decline in vision was the same as SOC. There are significant unknowns in the long-term efficacy of investigational AVXS-101, further amplified by the extremely limited number of patients who have received this treatment to date. In addition, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended.ⁱⁱⁱ
- In either the base case analysis or in the scenario analyses, ICER should assume that SMA patients treated with Spinraza will continue to improve (e.g., *increase* motor function) as observed in clinical trials results, such as the ENDEAR/SHINE analysis^{xii}, and reports from real-world practice. In ICER's current analysis, improvements observed in clinical trials and real-world practice are ignored and replaced with the incorrect assumption that patients do not improve from the health state they are in at the end of short-term clinical trials.
- The present ICER model fails to adequately capture clinically meaningful improvements and quality of life changes and relies on arbitrary assumptions about long-term efficacy. The proposed model health states are based on binary motor milestone achievements and are not sensitive enough to differentiate between changes in clinical or quality of life improvements that affect QALYs. ICER should alter its methods to allow for more sensitivity in QALY estimates for patients in different SMA health states reflecting 'no milestones', 'mild milestones', and 'moderate milestones'. For the long-term model, the base case analysis assumes that motor milestones achieved at the end of follow-up in clinical trials are sustained until death. This assumption is biased, as it conflicts with the trend of continuous improvement observed in patients treated with Spinraza and confers a durability of efficacy to investigational AVXS-101 that has yet to be proven.

4. Key assumptions in the draft assessment unduly disadvantage Spinraza, and important areas of uncertainty are not adequately addressed. Incremental cost-effectiveness ratio values are inappropriately presented as absolute numbers instead of ranges or intervals to account for uncertainty.

- Motor Milestones Achieved on Spinraza, Page 58: The estimated proportion of ‘sitting’ patients at different time points was based only on participants in SHINE who attended those study visits. Because the ENDEAR study was terminated early due to the favorable benefit/risk profile established at the interim analysis, not all patients were followed long enough to make it to latter study visit days in ENDEAR and SHINE. ICER disadvantages Spinraza in the multi-stage calculation process as shown in Table E2 and underestimates the proportion of patients in the ‘sitting’ health state by incorrectly using the number of patients at baseline as the denominator instead of the number of patients at the study visit (e.g. Day 698). ICER’s current approach does not produce an accurate estimate of patients achieving the ability to sit in the SHINE study.
- Long-term Assumptions, Page 61: ICER’s assumptions on QALY weights for different health states inadvertently apply a downward bias in the value of Spinraza while also overstating the value of investigational AVXS-101. In ICER’s current assessment, the ‘not sitting’ health state assumes the same overall survival of the ENDEAR sham control arm which recognized no treatment benefit. The ‘walking’ health state is also assumed to have the same overall survival of the US general population. Since a higher proportion of patients were in the ‘walking’ health state for the investigational AVXS-101 model, these optimistic assumptions were applied to benefit the incremental QALYs and cost-effectiveness ratio of investigational AVXS-101.
- Time Horizon of Long-Term Model, Page 55: ICER mentioned that the extrapolation of motor function milestones was conducted for the long-term model over a lifetime horizon. However, ICER excluded the exact number of years (e.g. 10 years, 20 years, etc.) that was defined as the lifetime horizon.
- Patient Utility Values, Page 64: The patient utility values for the different health states are key drivers of uncertainty and drastically impact the incremental QALY results. Patient utilities have the largest impact on cost-effectiveness results, especially for the later-onset model. ICER decided to use patient utility values from multiple references versus one study. ICER did not discuss or evaluate the key utility data (for Type I and II) from the Lloyd vignette study^{xiii} in its sensitivity analyses. Of the 3 available utility sources, the ERG preferred the vignette study according to the NICE committee papers August 2018.^{xiv}
- Treatment Costs, Page 65: Since investigational AVXS-101 is not yet approved by the FDA, its final market price is not yet available and remains highly uncertain. Many long-term costs of investigational AVXS-101 are unknown and sensitivity analyses should be conducted to understand the potential impact of downstream costs on treatment value. There is also large uncertainty regarding the long-term durability and safety of investigational AVXS-101. As there are limited data for investigational AVXS-101 with only 15 patients total, of which 7 have been reported to receive Spinraza post CL-101 trial, total treatment costs should consider inclusion of Spinraza as reported in the real-world.
- As suggested by ISPOR and NICE guidelines, robust methodologies include performing extensive sensitivity and scenario analyses to explore the impact of structural and input parameter uncertainty.^{xv,xvi,xvii}

5. The importance of Spinraza’s approval and evidence supporting the ability to treat broad and diverse patient populations is not accurately captured in the ICER assessment.

- **Later-onset (Types II/III)**: The safety and efficacy of Spinraza has been studied in patients with later-onset SMA (likely to develop Type II/III) in a randomized sham procedure-controlled Phase 3 trial (CHERISH).^{xviii} We believe the evidence rating of CHERISH should be ranked as an “A” (similar to ENDEAR) due to the significant and clinically meaningful efficacy of Spinraza that was demonstrated on measures of motor function (HFMSE, RULM) in a rigorously designed clinical study of N=126.

- Page 42-43: It is a failure and limitation of the ICER economic model to not capture any of the benefits of Spinraza versus SOC, as demonstrated in the CHERISH study, and acknowledged in ICER's own clinical assessment for later-onset SMA. These include a significant treatment difference of 5.9 points in total HFMSE score at 15 months in the interim analysis, and a clinically meaningful increase in RULM score from baseline to 15 months (4.2 vs. 0.5) for patients treated with Spinraza vs. SOC. These outcomes should be included in the ICER model as these assessments measure motor ability across domains that are meaningful to patients and important for activities of daily living. The current ICER model is incomplete without including these outcomes.
- Page 88: As mentioned by ICER and recognized by a key HTA body, the Type II/III model submitted by Biogen to NICE resulted in an incremental QALY difference for later-onset SMA: 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case.
- **Pre-symptomatic**: Patients with genetically diagnosed pre-symptomatic SMA (most likely to develop Type I/II) have been studied in the ongoing Phase II, open-label, multi-center NURTURE trial. The study has been presented at three different sources/conference proceedings.^{xix,xx,xxi}
 - Presymptomatic patients treated with Spinraza who were most likely to develop SMA Type I/II (median follow-up = 27.1 months) demonstrated unprecedented outcomes in the context of SMA natural history on event-free survival, motor function, and motor milestone endpoints.^{xxii}
 - NURTURE, a Phase II, open-label, **multi-center trial of N=25** pre-symptomatic infants, was determined as a "B+", a lower rating than open-label CL-101 for investigational AVXS-101.

6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients.

- Spinraza is used to treat over 6,000 patients worldwide and has become the foundation of care for individuals with SMA. Individuals with SMA live with an uncertain future and are among society's most vulnerable patients. Denying access to treatment can be life-threatening to patients.
- Spinraza has been approved for use in over 40 markets worldwide as of January 2019. The clinical benefit of Spinraza has been rigorously evaluated and validated by numerous other HTA bodies.^{xxiii}
 - **Germany**: First orphan drug ever with major added benefit & third product with major added benefit since AMNOG exists, out of 246 assessments.^{xxiv}
 - **France**: One of the few rare drugs to be recognized as bringing a high level of medical innovation, receiving an ASMR III for Type I and Type II.^{xxv}
- Economic modeling in rare disease is often challenging and frequently does not portray the full picture of the unmet medical needs of the community or adequately address how to objectively assign monetary value to quality of life.^{xxvi,xxvii} Many orphan medicines are not deemed cost-effective (determined by cost per quality of adjusted life year) based on standard accepted cost-effective thresholds. However, many key **HTA markets** (Germany, France, Australia, Sweden, Scotland, Canada/INESS) **recognize Spinraza's value** and have ensured access driven by clinical benefit and the robustness of the clinical data.

In addition to these points, we have outlined a total of 16 specific technical concerns and/or errors that we ask ICER to address in its revised report. Please see the Appendix for details related to these specific issues. Biogen thanks ICER for the opportunity to comment on the draft report. We would be happy to discuss any of the outlined concerns in more detail if needed.

Sincerely,
Chris Leibman
Sr. Vice President, Value and Access
Biogen

January 30, 2019
Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to respond to the ICER Spinal Muscular Atrophy Draft Evidence Report. Spinal Muscular Atrophy (SMA) is a progressive disease that has a profound impact, not only on those with the condition, but also on their caregivers. Despite recent clinical advances, there remain significant unmet needs in SMA. Genentech, in collaboration with PTC Therapeutics and the Spinal Muscular Atrophy Foundation (SMAF), is developing risdiplam, an investigational drug designed to modify survival motor neuron 2 (SMN2) splicing for the treatment of patients in all ages and stages of SMA.

Genentech believes the economic models in ICER's draft evidence report do not accurately reflect the totality of available data. We provide the following suggestions for your consideration:

- 1. The economic models should be revised in order to prevent oversimplification of the disease course and better capture treatment benefits important to patients.**
- 2. Model assumptions should be revised to adequately reflect high uncertainty due to lack of long-term outcomes data and limited evidence on utility and cost.**
- 3. Caregiver productivity and quality of life (QoL) should be included in all economic SMA models in order to reflect the true impact of disease and treatment to society.**

We provide detailed comments and evidence supporting our key recommendations in the remainder of this document.

- 1. The economic models should be revised in order to prevent oversimplification of the disease course and better capture treatment benefits important to patients.**

We believe the model structure, health states and assumed utility and cost values should be reconsidered in order to more accurately reflect outcomes meaningful to patients.

Infantile-Onset Model:

- The current model is based on permanent ventilation, death, and motor milestone achievement. Unless ‘sitting’ or ‘walking’ were achieved, the utility and health-state cost are assumed to be the same. Given the majority of patients in the ENDEAR trial did not achieve ‘sitting’ or ‘walking’, this model construct essentially ignores the benefits of delayed or circumvented permanent ventilation on patient and caregiver QoL.¹ Literature has showed that patients requiring ventilation had a lower utility score than patients who did not, despite not achieving any motor milestones.²
- In the base case of infantile-onset model, improvements in bulbar function and minor motor function improvements (e.g., head control, rolling, crawling, and standing) are not reflected. In clinical trials, an increase of ≥ 4 points in the CHOP-INTEND score is considered clinically meaningful and this was achieved by a large majority of treated patients in the ENDEAR and START trials.^{1,3} Even when the ‘sitting’ or ‘walking’ milestone is not reached, improvements in other motor abilities (e.g., head control and rolling), bulbar function (e.g., eating and speaking) and activities of daily living (e.g., moving and dressing) are clinically meaningful and are associated with QoL improvements for both patients and caregivers.⁴

Genentech encourages ICER to adjust the health state cost and utility value in the base case model. Applying different assumptions for permanent ventilation and ‘not sitting’ will reflect the lower level of support required as well as the improved QoL for patients not requiring permanent ventilation. To the extent possible, ICER should also apply additional utility benefit for improved bulbar function, achieving interim milestones (e.g., head control, rolling), and other functional improvements due to treatment.^{1,3,5,6}

Later-Onset model:

- The model structure includes only three motor milestones: ‘not sitting’, ‘sitting’, and ‘walking’. Although these milestones are convenient for linking to available data on health state utilities, these were not the primary endpoints in clinical trials. For example, none of the treated patients in the CHERISH trial achieved walking without assistance.⁷ However, an increase of ≥ 3 points in HFMSE is considered clinically meaningful and this was achieved in 57% of treated patients in the CHERISH trial.^{7,8} Such improvements would translate into improved functional ability and QoL, thus should be captured in the model. In addition, the ICER report concludes that Spinraza® (nusinersen) is dominated by best supportive care, with higher costs but no improvement in quality-adjusted life years (QALYs) or life years (LYs). This model result lacks clinical validity. Natural history suggests that as SMA progresses, patients lose motor functions and their ability to remain independent decreases over time.⁹
- Even in the absence of stark improvement in motor milestones such as ‘walking’, disease stabilization or prevention of further deterioration are important

improvements.^{4,10} A qualitative study demonstrated avoiding declines in function are important for patients and even small changes make a substantial difference for patients to function and thrive. As noted by a clinician in the study, *“the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized vehicle or not, and that can make a huge impact on their quality of life and on their ability to be independent.”*¹⁰

- Additionally, the mean age of patients with later-onset SMA in the economic model was assumed to be 2 years. While this mean age was based on the CHERISH trial population, it is not representative of the population in the real world. The Cure SMA membership database may be a better source for the age used in the model.¹¹

Genentech encourages ICER to explore an alternative model structure for later-onset SMA. The health states should be defined by patient functional levels that are meaningful to patients and caregivers (e.g., level of independence) and reflect the benefit of treatment. In addition, we also recommend revising the mean age of later-onset patients in this model to be more in line with the real-world population.

2. Model assumptions should be revised to adequately reflect high uncertainty due to lack of long-term outcomes data and limited evidence on utility and cost.

- While it takes time for the long-term effects for any new therapy to emerge, the optimistic assumptions around the durability of effect have created bias in favor of Zolgensma® (onasemnogene abeparvovec). This is likely due to the one-time administration frequency and the large magnitude of effect observed in a Phase I, single-arm study with a highly selected patient population (N=15). There are multiple key assumptions built into ICER’s base case evaluation, given the *“unknown duration of expression of the gene therapy”*.¹² Most notably, ICER assumed motor function milestones achieved at the end of the trial period are sustained until death. Additionally, it was assumed that Type I patients who achieved ‘sitting’ or ‘walking’ had mortality similar to Type II and Type III patients, respectively. However, despite motor milestone improvements, 5 out of 12 (42%) patients in the START trial (cohort 2) still required ventilation, an intervention not common for Type II or Type III patients.^{3,12} Moreover, 5 out of 12 patients treated with Zolgensma also went on to receive Spinraza after the end of the study period indicating a need for additional therapy in some patients.¹²
- In ICER’s model, key drivers of uncertainty are (1) monthly cost, (2) utility values for ‘sitting’, ‘non-sitting’, and ‘walking’, and (3) the length of survival associated with the ‘sitting’ and ‘walking’ health states for infantile-onset patients. Of note, none of these estimates are from clinical trials or robust observational studies. In many cases, proxy estimates and assumptions were used. These may have led to a low level of precision in parameter estimates, leading to further uncertainties surrounding model results.

- Lastly, cost and disutility of treatment-related adverse events should be captured in the model as those events are well characterized and distinct from disease-related complications. Similarly, cost and disutility associated with intrathecal administration should be accounted for. Specifically, facility costs associated with intrathecal administration, in both inpatient and outpatient settings, should be included.

Genentech recommends that ICER make the following adjustments to the models:

- (1) The short-term and long-term model results would be more meaningful, if presented separately. For the long-term model, it would be more conservative to adopt a 5-year or 10-year model horizon as the base case rather than lifetime horizon. A shorter time horizon would also be in line with ICER's last evaluation of a gene therapy (Luxturna™ [voretigene neparvovec-rzyl]) which applied a 10-year model horizon as the base case.¹³ Additionally, the lack of nationalized healthcare in the US makes the shorter-term horizon more relevant in payer decision making.
- (2) Revise the base case to assume a proportion of Zolgensma patients lose motor function over time based on the fact that ~40% of patients from the START trial subsequently received Spinraza.
- (3) Vary utility and cost parameter values by 20% instead of 10% in sensitivity analysis given the high level of uncertainty in the model.
- (4) Include the cost and disutility related to adverse events and the facility cost and disutility associated with intrathecal administration in the model.¹⁴

3. Caregiver productivity and QoL should be included in all economic SMA models in order to reflect the true impact of disease and treatment to society.

We believe that caregiver burden should be included in any cost-effectiveness analysis determining societal value. The impact of SMA on caregiver productivity and QoL is well documented in published literature.¹⁵ In this draft report, caregiver burden is excluded because ICER believes its inclusion may *“lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer”*.¹² However, in a cost-effectiveness assessment of pediatric interventions, incremental cost-effectiveness ratios on average decreased by 31% when family spillover effect was included.¹⁶ Genentech strongly recommends that ICER include caregiver burden by including productivity and QoL impact in the infantile-onset, later-onset, and pre-symptomatic models.

In closing, we thank you for the opportunity to comment on the draft evidence report for SMA. Despite the number of clinical advances in this rare disease, there continues to be a high unmet need due to ongoing challenges with access, logistics, and lack of clinical data in the broader SMA population.¹⁷ Genentech remains committed to therapeutic innovation

and engaging with ICER as they evaluate therapies for SMA patients. We hope these comments will contribute to a more robust assessment of the current and future therapies.

Sincerely,

A handwritten signature in blue ink, reading "Jan Elias Hansen". The signature is written in a cursive, flowing style.

Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
Genentech US Medical Affairs

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Comment to ICER on the draft evidence report: “Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value”

This detailed analysis relies on many assumptions and a very small sample size with limited duration of observation under treatment. The conclusions made in this report are fraught with uncertainty. While the goal of this ICER evidence report is certainly of high merit, it is premature to endorse the conclusions drawn by the authors. Later analysis of a larger sample of treated patients who are observed over a longer period of time will be of greater value.

Richard S. Finkel, MD
Nemours Children’s Hospital

Memorandum

Date: January 31, 2019

To: Institute for Clinical and Economic Review

From: Professor Emeritus Louis Garrison, PhD, The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy, University of Washington, Seattle WA 98195

Subject: Comments on Draft Evidence Report on Spinal Muscular Atrophy

Dear Colleagues,

Thanks for the opportunity to comment on ICER's draft evidence report on spinal muscular atrophy (SMA).

I am a health economist and Professor Emeritus in The CHOICE Institute at the University of Washington. I have participated as an independent consultant in a one-day health economics advisory board sponsored by AveXis, Inc., where high-level issues related to onasemnogene abeparvovec (Zolgensma[®], Novartis AG/AveXis) were discussed. I have not seen or reviewed any models that AveXis has developed for this product. I also received support from AveXis to prepare a conceptual, general thought piece on cost-effectiveness thresholds (CETs) for products for ultra-rare diseases with catastrophic health consequences, such as SMA. This article—coauthored with three colleagues, who are also consultants to AveXis—will soon be published as a viewpoint article in the Journal of Managed Care & Specialty Pharmacy.

I have long believed that welfare economic theory could provide a basis for a higher threshold for these ultra-rare, health catastrophic diseases, and that, in theory, the optimal threshold might vary among different diseases more generally. ICER has recently initiated a new effort on the topic of cures, and ICER staff interviewed me earlier this month, where I outlined my views. As I explained, this argument is related to the additional “novel elements of value” that were outlined in our recent ISPOR Special Task Force on Value Assessment Frameworks. In particular, I think that the additional elements—beyond the cost per quality-adjusted life years (QALYs)—of insurance value and severity of disease are key.

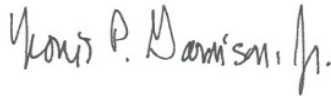
With regard to this SMA report, these arguments would suggest that ICER is being too conservative in applying a cost-per-QALY threshold of \$150,000 per QALY in projecting a “value-based price” (VBP) for onasemnogene abeparvovec. ICER does recognize a broader range for rare diseases of up to \$500,000 per QALY, and should consider, in this instance, either not making a specific projection for a VBP based on \$150,000 per QALY, or presenting it at a higher level or as a range with a higher upper bound. Given that onasemnogene abeparvovec has not been launched, the device of using “placeholder price” of \$2,000,000 is understandable. However, it may create misleading benchmark: for example, the U.S. Government values lives at closer to \$10 million (<https://www.transportation.gov/regulations/economic-values-used-in-analysis>).

L. Garrison
Jan. 31, 2019
Page Two

Furthermore, given the grave, negative implications of having a child with SMA Type 1 for parents and caregivers, ICER should emphasize the societal perspective. It was not clear to me whether the “Modified Societal Perspective” alternative in the report captures the “family spillover” effect, e.g., on the (dis-)utility of parents and caregivers. Of course, as outlined in our ISPOR report, augmenting cost-effectiveness analysis—beyond the cost-per-QALY—affects the calculation and/or interpretation of the appropriate CET.

I hope these comments are helpful. Please let me know if you have any questions. I would be happy to discuss further.

Sincerely yours,

A handwritten signature in dark ink that reads "Louis P. Garrison, Jr." The signature is written in a cursive, slightly slanted style.

Louis P. Garrison, Jr., Ph.D.
Professor Emeritus, The CHOICE Institute



Make today a breakthrough.

On behalf of Cure SMA, the largest patient group dedicated to the treatment and cure of spinal muscular atrophy (SMA), we appreciate the opportunity to comment on the Institute for Clinical and Economic Review (ICER)'s Draft Evidence Report entitled *Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value*.

We believe there is an important role for this type of analysis, which can assist in finding the right balance between preserving the incentives that are essential to attract investment and innovation to an orphan disease and not restricting access to approved treatments. We also believe such an analysis should place high value on the patient voice and perspective. It should contain accurate data from clinical trials and should be based on educated assumptions and knowledge about the disease under review. A selection of errors and issues that we have observed are presented in the categories below.

We request that ICER prominently and clearly include the specific disclosure of what they consider fair market value to be in an ultra-rare disease like SMA, as this is critical to interpreting this analysis. According to the framework for considering ultra-orphan drugs (such as Zolgensma and Spinraza) ICER adopted in 2017, this value is up to \$500,000 per Quality Adjusted Life Year (QALY).

Lack of Understanding About SMA:

Within the report are multiple errors showing a lack of basic understanding of the disease. For instance, the report states that "there remains considerable uncertainty in the generalizability of the results" (page 48). However, Spinraza clinical trials were completed in patients with SMA types I-III. SMA types I-III represents approximately 95% of patients with SMA. Due to the genetic homogeneity of SMA, the mechanism of action for Spinraza and Zolgensma is the same across the disease spectrum.

Additionally, this report does not seem to understand the basic biology of SMA stating on page 27 that "Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arm. The direction of potential bias in results is unclear as the patients receiving Spinraza may be at higher risk of death and other complications but may also have a greater potential to improve." The progressive loss of motor function is due to loss of motor neuron innervation. An important consideration for therapeutic efficacy is that motor neurons cannot be restored after being lost and this limits the time window allowing for maximal improvement.

The lack of SMA natural history understanding is reflected in the statement "we do not know how the 15 patients would have progressed if they had not been treated with Zolgensma." The most recent natural history studies consistently describe the progressive motor weakness and progression to respiratory failure and death without achieving the motor milestone of sitting (Finkel et al, *Neurology*, 2014; Kolb et al, *Ann Neurol*, 2017; [De Sanctis et al, NMD](#), 2016). In stark contrast, 11/12 infants treated with high dose Zolgensma achieved independent sitting and all have survived without permanent ventilation (Mendell et al, *NEJM*, 2017).

The long-term extrapolation model for non-sitters is flawed. The long-term model utilizes a lower mean survival of 1.55 years for non-sitters compared to a mean survival of 5.3 years for permanent ventilation

thus assuming significantly poorer survival for non-sitters compared to permanent ventilation, even though the non-sitter group has showed better outcomes and improvements following treatment with Spinraza. The ENDEAR trial demonstrated a 47% reduction in the risk of death or permanent ventilation in the Spinraza treated group compared to control (Finkel et al, NEJM, 2017). The life years for the SMA type I not sitting Spinraza treated model is severely underestimated.

Inaccurate Clinical Trial Data:

Throughout the report, clinical trial data is misinterpreted in the ICER models, which has a major impact on the determination of cost effectiveness of the therapies under evaluation. Table 3.4 of the report correctly indicates that maximally 29% of patients had the ability to sit independently towards the end of the SHINE extension study (Castro et al, NMD, 2018). However, in section 4 of the report a value of only 11% is used. This lower value appears to be calculated using the total number of patients receiving Spinraza in the ENDEAR trial (n=81, Finkel et al, NEJM, 2017), rather than the number of patients being assessed at that particular time point (n=31, Castro et al, NMD, 2018). By doing so, the model unfairly assumes unfavorable outcomes for the unassessed 50 patients, i.e., none would have sat if assessed. Meanwhile, the actual reason that many in the full cohort were not assessed at this time or beyond is that they had not yet reached this point in the study (meaning that they had been on drug less time than the actual timepoint under evaluation).

Furthermore, there are major flaws in framing the outcomes of pre-symptomatic treatment with Spinraza, which downplay the dramatic impact on survival and function in this situation compared to natural history. Trial data demonstrate that most infants treated proactively, when free of symptoms, achieve the motor milestones of walking and standing. In fact, 22 of 25 were able to walk with assistance and 17 of 25 were able to walk independently (Swoboda et al, WMS, 2018). To date, no pre-symptomatic SMA infant treated with Spinraza in this study has died or required permanent ventilator support. The assessment of pre-symptomatic treatment benefit is wrongly framed by a comparison to the development of healthy children. Natural history outcomes regarding individuals with the same SMN2 copy number should be used for comparison, not outcomes in unaffected children.

Finally, as with any treatment whose approval is based on clinical trials of a feasible and ethical duration, there is always ongoing uncertainty about longer-term outcomes. However, the report has a lengthy section (3.4) about clinical trial controversies that seems unwarranted. These would be better framed as important issues that would ideally now be examined using real world data capture on drug efficacy and safety. We believe ICER should frame long-term uncertainties in a more balanced manner, leaving open the possibilities of both pessimistic and optimistic scenarios for future results. Currently, for example in tables 4.21 and 4.22, there are only 2 and 3 positive scenarios modeled out of the total in each table.

Lack of Patient Perspective:

This analysis is further weakened by its lack of patient perspective. This lack of patient perspective is vastly different from current approaches to the drug approval processes and safety protocols at the FDA, research priorities and protocols at the NIH, and the philosophy reflected in recent milestone legislation, the 21st Century Cures Act.

ICER assigns benefit to the patient only if the drug allows for obtaining milestones such as sitting or walking. Meanwhile patients have reported, and the FDA has recognized, the great value in abilities that

allow for more independence and activities of daily living (McGraw et al, BMC Neurol, 2017; and Rouault F et al, NMD, 2017). For some patients and their families, simply not getting worse is an improvement and a meaningful outcome. It should also be noted that even incremental increases in a patient's motor abilities may alleviate the stresses and challenges involved in caregiving by allowing patients greater ability for self-care.

These meaningful and valued milestones are not factored into this analysis; however, the complete set of clinical trial data from the early open label studies to the pivotal ones demonstrates these improvements in SMA type I, II, and III participants.

Infants who received Spinraza in the ENDEAR study showed statistically significant improvements in HINE-2 response compared to sham control at both the interim analysis (21/51 [41%] of Spinraza and 0/27 of sham control group; $p < 0.001$), and in the final analysis (37/73 [51%] of Spinraza and 0/37 sham control patients). In the Spinraza group, 22% of the infants achieved full head control, 10% were able to roll over; in the control group no infants achieved these milestones at the end of the entire study. The percentage achieving head control increased to 45% on day 578 for those continuing into the SHINE extension study.

There were also improvements in participants' CHOP-INTEND scores in this study. Seventy-one percent of infants treated with Spinraza achieved an increase of ≥ 4 points in CHOP-INTEND score between baseline and their end-of-trial visit (Table 3.3); compared to just 3% in the sham control arm who achieved improvement.

In the CHERISH study, the prespecified interim analysis from baseline to month 15 showed a 4 point increase in the HFMSE score in the Spinraza group and a 1.9 point decrease in the control group (Mercuri et al, NEJM, 2018). This represents a difference in ability to perform three items on the Hammersmith scale between the treatment and sham groups, whose items have been shown to be correlate to activities of daily living. In the final analysis, 57% of the children in the Spinraza group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points.

We know that most patients show clinically meaningful improvement with Spinraza, yet ICER ignores these when constructing this analysis. This lack of patient perspective about the value of these milestones and incremental improvements seriously weakens ICER's models, and therefore, the analysis of value and efficacy is incomplete. It is a disservice to all with SMA that a report which could impact access to life saving treatments for some of the most vulnerable members of society does not include their perspective.

The ICER models show that only 1% of SMA patients gain any meaningful benefit from Spinraza. This ignores and contrasts with:

- 51%, vs 0% untreated, HINE Responders.
- 45%, vs 0% untreated, with Head Control.
- 71%, vs 3% untreated, CHOP Responders.
- 57%, vs 26% untreated, HFMSE Responders.



Make today a breakthrough.

The process of determining QALYs for patients permanently on ventilators and those who are non-sitters appears arbitrary and does not take into account the wide range of patient outcomes in between these two statuses. The analysis also fails to take into account the advances in technology that have made it possible for physically limited individuals to meaningfully contribute to society in ways never before possible. Many patients who have not achieved the arbitrary ICER chosen milestones are productively employed.

Moreover, incorrect assumption and subsequent erroneous modeling occurred around the fact that some subjects who received Zolgensma in the START trial were subsequently treated with Spinraza. The assumption that Spinraza was added after Zolgensma due to a deteriorating health status led to modeling that “half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth ($33\% \times 50\%$) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period.” There is no evidence to support this assumption. The more likely explanation is that families’ expectations are high for best outcomes and families will do everything possible to get their child every available treatment in order to eliminate as many symptoms as possible.

Bias in ICER Model for Financial Discounting of Life Years:

For a pediatric and typically fatal disease such as SMA, now with transformative and impactful treatments, the ICER model of financially discounting life years has a significant effect. The controversial approach of using a financial model for discounting life years (prior to any utility discounting) should be clearly disclosed and have scenario analyses to indicate the impact on any conclusions.

These groundbreaking treatments for SMA are taking an untreated lifespan of less than 2 years up to over 30 years for Zolgensma, and also up to over 60 years for Spinraza in pre-symptomatic patients. ICER does a present value financial reduction on these actual life years to drastically reduce these extraordinary results to 18 and 27 discounted life years respectively.

In addition, as ICER states, the use of QALY can discriminate, and we agree: “...and viewing results of both the cost per LY gained and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group.”

The conclusions in this report will change significantly based on the above notes and whether an actual life years are discounted or not.

Summary:

This report is based on assumptions from ICER that the currently approved treatment for SMA provides a meaningful benefit to only 1% of the SMA population. It should be noted that this is separate from any analysis of whether any benefits are worth the related costs. This is in stark contrast to the FDA analysis and approval for 100% for all ages and all types of the disease. ICER decides that SMA types II, III and IV gain no benefit at all from the only currently approved treatment for this devastating disease.



Make today a breakthrough.

As currently drafted, including numerous and substantial errors in both data and assumptions and modeling, and a disregard for the SMA patient and caregiver perspective, we believe that this report should not be used by any groups or individuals for SMA treatment related decisions.

Sincerely,

A handwritten signature in black ink, appearing to read "K. A. Hobby".

Kenneth Hobby
President



Make today a breakthrough.

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January 31, 2019

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Submitted electronically to: publiccomments@icer-review.org

Dear ICER Review Panel,

Thank you for the opportunity to provide comments on the *Institute for Clinical and Economic Review's Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value Draft Evidence Report* as published December 20, 2018, hereinafter "the draft report".

As an organization with a mission of transforming the lives of individuals affected by SMA and other neuromuscular diseases through innovations in science and innovations in care, the Muscular Dystrophy Association (MDA) is committed to funding groundbreaking research; accelerating the development of treatments and cures; promoting early identification, diagnosis and treatment; and improving health outcomes. For more than 65 years, MDA has been on the frontlines of research for SMA and other neuromuscular diseases. We funded foundational work in SMA and invested in the early-stage development of nusinersen (brand name Spinraza). We also helped to connect SMA patients with clinical trials for onasemnogene abeparvovec (brand name Zolgensma), and we are encouraged by the promise of this innovative new gene therapy, the first of its kind for neuromuscular disease treatment.

This is a pivotal time for the SMA community. Only a few years ago, there were no treatments for SMA. Now, we are on the cusp of having more than one treatment option. This paradigm shift is a reason for hope and excitement. In the absence of therapy intervention, death or the need for constant ventilation to breathe before the age of two years is the outcome for more than 90% of individuals diagnosed with SMA Type 1. Considering that SMA is the number one genetic cause of death for infants, affecting approximately 1 in 10,000 newborns in the U.S. each year, and accounting for the severity of the disease, the recent therapy developments and potential advancements mark important progress for not only the SMA community, but for society as a whole.

The importance of the evolution from having no treatments to having treatment options cannot be overstated, and any effort to evaluate the respective therapeutic approaches must

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be thoughtful and measured and should help support access to novel and life-changing and -saving therapies.

SMA is a lethal disease that affects the motor nerve cells in the brain stem and spinal cord and carries a significant burden. The age at which SMA symptoms begin roughly correlates with the degree to which motor function is affected: the earlier the age of onset, the greater the impact on motor function. For this reason, MDA advocated for SMA to be added to the national Recommended Uniform Screening Panel and continues to work with states to encourage them to add SMA to their list of diseases for which infants are screened at birth. With the implementation of newborn screening for all babies born in the US, infants with SMA will have the opportunity to receive treatment early, before critical motor function is lost, allowing the future of the disease course and clinical care approaches to be altered.

For MDA and the patient community that we represent, the development of therapies for rare diseases like SMA is of paramount importance. We appreciate that there is a value framework from which to consider therapies and appreciate ICER's intent to provide a value-focused lens through which to consider therapies for SMA and other neuromuscular disorders.

With regard to the value of treatments for SMA as set out in the draft report, we would note that the evaluation of milestones may not fully reflect the experiences and needs of the patient community. For example, gains in mobility, such as the ability to sit or to reposition unassisted, can represent significant, positive change in the life of an individual living with SMA and their caregivers. Improvements in mobility, however small they may be deemed, often represent major improvements in quality of life and the value of these gains cannot be discounted. In addition to health improvements that may be associated with increased mobility, increases in mobility are directly related to independence, which is a critical factor for those living with neuromuscular disease. Similarly, respiratory function is also a major concern for the SMA community. The significance of what one may consider even relatively small gains for SMA patients in this area must be reflected in any evaluation. Further, with SMA being classified as not only a rare disease, but as an ultra rare disease with a significant burden, the QALY applied in the report is likely insufficient. This is important as such determinations may impact access to treatment. Additionally, while the report notes that there are "common limitations" in applying the framework in rare diseases, there are further limitations in the draft report as Zolgensma has not yet received FDA approval. Thus, for example, it does not yet have a price. Similarly, and as noted in the report, there are no coverage policies associated with Zolgensma to evaluate.



Given the importance and potential impact of a value framework on the SMA community, including the role that such findings may have on payor determinations and behavior, we appreciate the opportunity to comment, and look forward to the opportunity to engage with you further as you finalize the report.

Sincerely,

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January 31, 2019

Steven D. Pearson, MD, MSc, FRCP
President
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RE: Draft Evidence Report “Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER’s December 20th Draft Report, “Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value.”

Before commenting on specific aspects of the Spinal Muscular Atrophy (SMA) Draft Report, we want to revisit some past ICER reports and comments – and particularly responses to some of our previous comments, since they provide critical insights into ICER’s approach to health care challenges, and ICER’s perceived role in attempting to inform decisions about innovations.

Because imprecise language can lead to misleading conclusions, the specific issue we want to address is ICER’s decisions about choices regarding word usage and phrasing to describe its work. The danger of such rhetorical imprecision is well summarized in this quote: “[Language] becomes ugly and inaccurate because our thoughts are foolish, but the slovenliness of our language makes it easier for us to have foolish thoughts.”ⁱ

Specifically, in responding to our comments on the Opioid Use Disorder Draft Report, ICER noted that its use of the term “healthcare” rather than “health care” “does not affect the conclusions of our report.”ⁱⁱ While in that specific instance the meaning is likely the same, that is not always true. For example, the two phrases “mental healthcare” and “mental health care” have two distinct and different meanings. And we are very concerned that ICER apparently fails to recognize that such differences can lead to misinterpretation of data or results.

This concern is even more problematic in the Final Report about OUD treatments where ICER equivocates on the definition of MAT, declares that its assessment MAT can have two different

meanings, and that ICER will use them interchangeably.ⁱⁱⁱ In that report ICER also misconstrues and misrepresents the meaning of the statement from the FDA: “Because OUD is a chronic illness, we should consider treating it much like we would any other chronic condition. We do not think of the medications used to treat diabetes or hypertension as ‘medication assisted treatment.’ We simply call it ‘treatment.’ OUD should be viewed similarly.”^{iv} First ICER fails to understand that the FDA is not questioning the meaning of the definition of MAT - the heading for the article in fact is “Medication Assisted Treatment.”

Second, ICER fails to appreciate that the FDA is reinforcing the point that “It is important to remember that MAT is broader than just the use of medication,” which is completely contrary to the meaning of narrower term, “Medications for Addiction Treatment.”

Third, the point the FDA is making in comparing treatment of OUD to diabetes and hypertension is that RESPONSIBLY treating people with OUD, diabetes, or hypertension should ALWAYS involve not just medications, but also counseling of some sort. For example, clinician who prescribes a medicine to control blood sugar levels for a person with diabetes without support or counseling regarding diet, weight loss (or control), and exercise would be grossly negligent. ICER’s failure to recognize what the FDA is saying and the fundamental difference between “Medication Assisted Treatment” and “Medications for Addiction Treatment” – reflects ICER’s siloed (and flawed) vision that focuses on pharmaceuticals both clinically and economically without putting that information into a comprehensive patient-centered context, is of course, extremely troubling and should cause all decision makers to have grave concerns about ICER’s entire activity-set.

And finally, ICER’s straw-narrow approach is retrograde to the movement of the U.S. health care system that is seeking to incorporate more comprehensive, integrated, and systemic analyses and innovations in care delivery, financing, and reimbursement as part of the broad trend to align all components of health care for better patient-centered clinical and economic outcomes for the benefit of patients, payers, and society.

ICER’s approach reflects a top-down centralized-control mentality that is reminiscent of the Soviet Union or a government agency with strict silo budget allocations that cannot be adjusted based upon clinical needs or new information. And history has shown the adverse outcome from this type of centralized and siloed thinking, planning, and management leads to society’s needs not being met because of inefficiencies, and mismatched production and distribution activities.^v

It is hard to know where to start in commenting on the specifics of the Draft Report for SMA since it includes 1 FDA approved medicine (Spinraza) that is given repeatedly, 1 potential treatment (Zolgensma) that could be curative (i.e., possibly a 1-time gene therapy treatment) that has not yet been approved by the FDA and acts through a different biological mechanism, and a “Drug X”^{vi} that is completely hypothetical with conjectured “data” and scenarios. We agree that “naïve comparisons should be avoided,”^{vii} but by producing a report about two distinctly different treatment approaches, ICER seems to be doing exactly that.

As we’ve previously stated, “evaluating the clinical and market potential of medicines prior to

approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult.”^{viii} In the Draft Report ICER has taken an additional leap to include a completely fictional construct. Therefore, we think it would be analytically and socially responsible for ICER to reissue an updated Draft Evidence Report that includes actual data for Zolgensma after FDA approval when its labelled indications and warning will be known, as well as the list price – and of course separately publish any fictional constructs of potential medicines in more appropriate publications.^{ix}

Our more specific comments about the December 20th Draft Report are organized below into sections concerning: Patient and Family Perspectives and Issues; Relationships Between Payment Policies and R&D Investments; ICER’s Pricing and Market Assumptions, and Additional Points.

Patient and Family Perspectives and Issues

Families and patients with SMA should welcome new treatments since if SMA is untreated “causes irreversible degeneration of motor neurons, which clinically manifests as progressive muscle weakness such that patients may have difficulty moving, swallowing, or breathing,”^x and life expectancy can be as short as 2 years depending on the severity of the disease. In addition, as the Draft Report describes, SMA is a disease with many forms based upon the specific genetic variations and the presence of the number of copies of the SMN2 gene that is associated with modulated severity and age of onset of SMA.

We also note that SMA does not affect cognitive functioning. Therefore, the preservation of motor function – or reversal of lost function – is important for self-care and autonomy of individuals with SMA, and ultimately their ability to earn a living and be productive members of society. In this regard, we agree that in ICER’s analytical scheme the “utility value” for individuals able to walk should be the same as the general population.^{xi}

While the genetic cause of SMA is known, and tests for determining a patient’s status are available, we share ICER’s concern about the limited data available about Spinraza and Zolgensma. However, models or projections based on uncertain data is inherently an error prone process and a fundamental flaw in this Draft Report, as well as many other ICER activities. The 189-page Draft Report^{xii} contains numerous references to this uncertainty, including the admission on page 183 that “the true uncertainty is likely to be more than that represented in our probabilistic analyses.” Nevertheless, the Draft Report makes economic declarations that it clearly recognizes others will rely upon for decisions affecting patients and families.^{xiii}

We also appreciate the complications of modeling based upon clinical trials that are single armed or limited in duration. However, for certain innovations, single arm trials are the appropriate structure and research methodology. As has been written, “Such comparisons [in a single arm study to the natural history of the disease] are meaningful only when the expected outcomes in the absence of the intervention are well-known, and the expected effect size from the intervention is large,”^{xiv} which clearly is the situation with Zolgensma.

Similarly, projecting long-term outcomes from trials of limited duration is a well-recognized issue in clinical research. However, this issue has largely been settled, since waiting for lifetime

results (i.e., 60+ year trials) is impractical, would deny patients access to treatment that have demonstrated short or intermediate term benefits, and would also effectively terminate any investments in such research.

Overall, the objections ICER raises about the sparsity of data are due to the self-determined timing of ICER's activities (i.e., before or shortly after FDA approvals) rather than the realities of the data itself. This is akin to a paraphrase of the Heisenberg Uncertainty Principle,^{xv} i.e., the sooner you get the data, the more uncertainty there will be, and conversely the more you demand certainty of data the longer you will have to wait - and more people and society will be denied the benefits of the resulting innovations.

Thus, while families and patients with SMA would clearly benefit from better treatment options, we believe that ICER's Draft Report – both its technical aspects and overall approach – are counterproductive to that goal.

Relationships Between Payment Policies and R&D Investments

We have previously commented to ICER about the relationship between payment policies (which include pricing and reimbursement schemes from payer) and R&D investments.^{xvi} While we continue to be befuddled that ICER's framework does not consider how payer decisions effect R&D priorities and resource allocations, we would like ICER to comment on the perspectives of two economists in an article^{xvii} in a Boston-based publication that notes how some funders of early and cutting edge research areas have greater flexibility for reassigning funding among potential types of projects and companies, including specific disease areas or patient populations, which they describe as “mobility of investment capital.”

While we await those comments from ICER, we continue to be concerned about ICER's lack of attention to this relationship because if policies and reimbursement practices fail to recognize it, the long-term consequences would be fewer treatment options, and higher morbidity and mortality. For example, observers of biomedical innovations and access to medicines have noted the recurrent problem about the availability of new antibiotics, (i.e., every 15 years or so there has been another call for the development of new antibiotics as resistance rises for older classes), but with little recognition that appropriate payment amounts and practices for new antibiotics should be part of the discussion. In this vein, the development of new antivirals likely took a step backward because of the rhetoric around the new treatments/cures for chronic hepatitis C infection in 2014, which interestingly almost never include information about how manufactures of two medicines approved by the FDA in 2011 for chronic hepatitis C infection took them off the market after only a few years because they had become clinically irrelevant.^{xviii} Extending this discussion, we also hope that ICER will incorporate this knowledge into its processes for ultra-rare conditions by eliminating the pointless request for information about R&D and manufacturing costs since that information only has a relationship to the price of a medicine in a fictional “truthy” world.”^{xix}

ICER's Pricing and Market Assumptions

ICER's assumption filled process fundamentally risks incorrectly modeling the real world. For example, it is widely recognized that modeling of uptake and usage of new medicines can be very far off from what actually occurs once a treatment is approved by the FDA. This was

evident from the actual usage of the first new medicines to treat hepatitis C (which had initial usage much greater than had been projected), and those to treat very high cholesterol because of PCSK9 protein variants (which had initial usage that was much less than projected). What is also interesting in both those cases was that over time, there was dramatic decline in the net prices paid by payers, although what patients paid may not have fallen to the same extent – which is of course an ongoing concern – and a factor ICER also does not address in its framework process.

We would appreciate ICER’s comments about how its methodology does not account for such real-world market dynamics that effect prices and overall costs to payers, patients, and society.

Additional Points:

- The Draft Report provides a link to the list the stakeholder from whom ICER requested input^{xx}, but not those from whom it actually received input. That list should be provided.
- The Draft Report only lists one “Expert Reviewer,” and that individual appears to have only a few years of experience since finishing her doctorate.
- The Draft Report states that “Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the SMN2 gene; Humana states that patients may have no more than two copies.”^{xxi} Can you explain the rationale for why different insurers would have such opposite prior authorization criteria? Also, Humana appears to have updated their criteria so that individuals with Delayed Onset SMA can have “no more than three copies of SMN2”^{xxii}
- It seems the 100% survival rate for Zolgensma has now been reported at 24 months.^{xxiii}
- One source for health care costs used for the scenario analyses are from the Department of Defense,^{xxiv} which are likely very different from overall U.S. health care costs.

Conclusions & Recommendations

Patients Rising Now remains concerned that ICER’s activities will continue to lead policy makers, and others (including payers and clinicians) to focus on limited data and suspect economic analyses to erect barriers to patients accessing FDA approved treatments, which would contribute to more adverse outcomes for patients. Such an outcome is compounded by ICER’s lack of transparency about its modeling, which includes an overly simplified and homogenized construct of the U.S. health care financing, delivery, and innovation systems and organizations.

Patients Rising Now believes that ICER’s Draft Report on SMA inadequately reflects patients’ perspectives, misunderstands how investment decisions for biomedical R&D are made, and by ignores market processes. Because the outputs from models are only as valid as the certainty of the data and the assumptions used to build the modes, the Draft Report’s conclusions are warped and inaccurate. Thus, the Draft Report’s “conclusions” have serious flaws and misleading, and ICER should reissue the Draft Report once more substantive and certain data is available.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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- ⁱ “Politics and the English Language,” George Orwell, 1946.
- ⁱⁱ ICER’s Response to Public Comments on Draft Report, “Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder,” October 25, 2018, p. 20
- ⁱⁱⁱ “Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder,” Final Evidence Report, December 3, 2018, p. 1
- ^{iv} “CDER Conversation: Treatment for Opioid Use Disorder,”
<https://www.fda.gov/Drugs/NewsEvents/ucm611659.htm> (page last updated July 18, 2018)
- ^v “Soviet food shortage not for lack of output. Distribution, waste blamed for problem,” Baltimore Sun, December 20, 1990, <https://www.baltimoresun.com/news/bs-xpm-1990-12-02-1990336114-story.html>
- ^{vi} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. 86
- ^{vii} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. 49
- ^{viii} Patient Rising Now’s Comment Letter to ICER about “Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value” Draft Evidence Report, September 20, 2018
- ^{ix} We would suggest “Weird Tales” (<https://www.weirdtales.com/>), or “Asimov’s Science Fiction” (<https://www.asimovs.com/>)
- ^x “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. 8
- ^{xi} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. 64
- ^{xii} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, pages 11, 22, 48, 49, 68, 72, 73, 81, 83, 86, 88, 90, 91, 93, and 183. In addition, there are numerous assumptions made in the report that add to the uncertainty of the Draft Report’s conclusions.
- ^{xiii} <https://icer-review.org/morning-view/04-27-18/>
- ^{xiv} “Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews, AHRQ Publication No. 13-EHC007-EF, January 2013
- ^{xv} <https://www.britannica.com/science/uncertainty-principle>
- ^{xvi} Patient’s Rising Now Comment Letters about ICER Draft Reports, “Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value” Draft Evidence Report, September 20, 2018, “Modulator Treatments for Cystic Fibrosis: Effectiveness and Value,” April 12, 2018, and “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value,” August 17, 2018
- ^{xvii} “Drug pricing conversations must take the cost of innovation into consideration,” Garthwaite and Ippolito, STAT, January 11, 2019. <https://www.statnews.com/2019/01/11/drug-pricing-conversations-include-cost-innovation/>
- ^{xviii} Incivek (approved by the FDA in May 2011) removed by Vertex in October 2014, and Victrelis (approved by the FDA in May 2011) removed by Merck in January 2015
- ^{xix} Stephen Colbert has been credited with giving new meaning to the word “truthy,” i.e., “concepts or facts one wishes to be true, rather than concepts or facts known to be true.”
https://www.american dialect.org/truthiness_voted_2005_word_of_the_year, also see
<https://www.nytimes.com/2010/10/17/magazine/17FOB-onlanguage-t.html>
- ^{xx} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. iv
- ^{xxi} “Spinraza® and Zolgensma® for Spinal Muscular Atrophy,” Draft Report, December 20, 2018, p. 19
- ^{xxii} http://apps.humana.com/tad/tad_new/Search.aspx?criteria=spinraza&searchtype=freetext&policyType=both (Accessed Jan 7, 2019)
- ^{xxiii} <https://www.novartis.com/news/media-releases/novartis-announces-fda-filing-acceptance-and-priority-review-avxs-101-one-time-treatment-designed-address-genetic-root-cause-sma-type-1>
- ^{xxiv} Armstrong EP, Malone DC, Yeh W-S, Dahl GJ, Lee RL, Sicignano N. The economic burden of spinal muscular atrophy. *Journal of medical economics*. 2016;19(8):822-826.

Institute for Clinical and Economic Review
RE: Public Comments (Spinal Muscular Atrophy)

To the ICER SMA group and other interested parties:

Today, for the first time, our son Max rolled over (unassisted) from his back to his side. Most babies do this when they are a few months old. Max is five. He has SMA type I. Max started receiving Spinraza in April of 2017. Since then, he has made significant gains:

- an eighteen point gain on the CHOP-INTEND (measured in clinic)
- louder vocalizations
- stronger wrist movements and greater hand and finger dexterity (allowing him to consistently control his communication devices and pilot his power wheelchair)
- being able to roll his head and slide his legs up and down when lying
- being able to turn up both corners of his mouth into the slightest hint of a smile

Since first receiving Spinraza, Max completed preschool and began attending kindergarten, all from home via a telepresence robot (which he pilots using two adaptive switches on his power wheelchair). Currently, in school, he is mastering his letters, learning basic arithmetic, writing stories, and exploring science and social studies. Meanwhile, in physical therapy, he is working on using his biceps and shoulders to lift his arms off the ground, using his neck to prevent his head from falling, and more.

Since Max began receiving Spinraza, we have seen greater energy and a boost in his ability to achieve the goals set for him in physical therapy. For us as his parents, this is deeply heartening. We have elected to schedule an orthopedic surgery (a bilateral screw hemiepiphysiodesis) that has recently become a part of the standard-of-care for SMA type 1 due to long-term benefits over a span of time previously considered well out-of-reach for the typical SMA type 1 patient—another example of the changes in care and opportunity brought about by the first wave of treatments for SMA.

As parents of a child with a rare, life-threatening disease, we had long reconciled ourselves to the importance of not taking the future for granted and making the most of each day. When a treatment first came within reach, we did everything in our power to ensure that Max began receiving it so he could reap the benefits as soon as possible. To us, the potential for long-term health and strength more than justifies the effort required to keep up with his Spinraza treatments. Ensuring that Max receives Spinraza is part of our definition of doing everything possible to give our child every opportunity. Significantly, it also gives us hope that when the

next, better treatment comes along, Max will be in a better place to derive benefits from it as well.

We hope these comments are helpful and thank you for the work you are doing to quantify the effectiveness and value of SMA treatments.

Sincerely,

Jonathan* and Kristen Lasko
maxstrength.org

*Jonathan Lasko serves on the Events and Family Support Committee of Cure SMA.

Hello,

August 10, 2011 was the first time we ever heard the words Spinal Muscular Atrophy (SMA). This would be a date that forever changed our family. Those three letters shattered our world and gave us no hope for our future. On that date there was no treatment or cure for SMA, only a death sentence, often delivered by doctors as a “take him home and love him, as he won’t see his second birthday” type of message. This was the message we were given to our then 1-month old first born, Mateo, who is now 7 years and 6 months old!

The first year of Mateo’s life was full of tears, 911 calls and constant fear of losing him. By his second year we were more comfortable with our new life with SMA and began traveling and getting more involved in things. SMA would rob Mateo of many things, including his ability to swallow, breathe on his own, move and smile. Mateo had surgery at 3 months old for a g-tube as he could no longer safely eat orally. At 7 months old Mateo had a tracheostomy as he could no longer breathe on his own and we had nearly lost him more times than any person should ever encounter. Over the months, Mateo would slowly start losing his ability to move his hands and feet. Mateo never had any head control and was often described as “floppy” by the doctors. Mateo’s cry was very weak and soft. Despite Mateo losing the ability to move he never lost the ability to fight. He continued to prove doctors wrong every time we celebrated another birthday. Mateo started school at 3 years old as cognitively he functioned right at his age level. Today Mateo is thriving in 1st grade where he loves being the center of attention.

We eventually decided we wanted to add to our family and decided to risk the 1 in 4 chance we would have another SMA child.

On January 24, 2016 Javier entered the world and he would help change SMA. A clinical trial was recruiting with a drug called Nusinersen. This drug would be delivered via lumbar puncture to replace the missing protein in SMN2. We took the chance of the unknown and Javier was enrolled in a trial at Johns Hopkins Hospital in Baltimore, receiving his first injection at 12 days old. Javier began meeting milestones that SMA type 1 children could never do. Javier drank from a bottle without choking, he maintained oxygen saturations, he eventually learned to roll over, sit up, crawl and eventually walk! We were originally told Javier would most likely be very similar to Mateo. What we have experienced is quite the opposite thanks to Spinraza. My husband and I had to learn to baby proof the house, something that was not needed for Mateo as he can’t move. We got to hear the words “Mama” and “daddy” for the first time, something Mateo has never been able to do as he cannot talk.

Javier still has development delay as he has poor core strength, making it harder to get up from the ground on his own. He can not jump or run. He receives weekly PT and OT sessions as well as wears braces on his feet. Javier does at times struggle with maintaining his oxygen above 92 when he is sick. He wears a bipap when ill. This compares nothing to what we’ve been through with Mateo.

On December 23, 2016 this drug was FDA approved. Despite it being FDA approved Javier's trial is still open for another two years, therefore he continues to travel to Baltimore every 4 months for injections. The down fall to this treatment is the every 4 month spinal injections. Javier has great anxiety when around doctors or hospitals. He is now at an age where he knows when we get to the hospital he will be getting an injection. I can only hope this will not be a lasting trauma response for him and he will understand when he is a bit older how important these injections are to him.

Mateo began receiving this drug on October 3, 2017. He has begun to get movement back in his hands and feet and a small curl of his mouth his back to indicate he is smiling! Mateo's oxygen levels have been consistently higher. He is able to recover from illnesses faster.

With all the excitement we were seeing in our boys we decided our family was not complete and we yet again rolled the genetic dice and got pregnant with our 3rd SMA baby. Amelia entered the world on March 30, 2018. Amelia began treatment of SMA at 11 days old. She is developing on target for her age and at this time needs no medical intervention. She can current sit unassisted, army crawl and is bearing weight on her legs. Amelia makes sounds and loves to try new foods. She has battled two colds at home with no concerns.

All our children are thriving due to research and advancements made in the last 7 plus years. It has been amazing to see how far the treatments for SMA have come as we get to experience them on a daily basis.

Thank you,

Amy M.

Date: 01/16/2019

1. Briefly describe your disease experience, including your diagnosis, treatments you've used, etc. Be as specific as you feel comfortable with.

My son was diagnosed with Type III, Spinal Muscular Atrophy (SMA) at the age of two. Overtime, he began losing the ability to walk. By four years old, he had his first manual wheelchair. He started Spinraza over a year and a half ago when he was five years old.

2. How do the disease/condition and the available treatments affect your day-to-day life?

Before we started treatment a year and a half ago, we observed our son losing the ability to walk. He was not able to lift his legs up while laying down nor was he able to stretch his leg outward while sitting. While standing, he was not able to bend his knees (squat) without falling. He fatigued easily (three to four hour naps were common) and fell frequently.

Since my son started Spinraza, he has gained and maintained strength. Before he started treatment, he was only able to walk 50 meters in a 6-minute walk test and fell six times during the test. Just over a month ago however, in the same 6-minute walk test, he was able to walk 150 meters without falling. This is incredible because by definition, SMA individuals (without treatment) lose muscle strength over time.

This translates to everyday living with respect to being independent. It means my son does not need an aide at school to take notes or use the restroom. Likewise, it means he can be independent at home performing daily tasks such as getting dressed, eating, using the bathroom and brushing his hair and teeth.

Spinraza has not only given my son the strength he desperately needed but the treatment has also given him more energy which allows him to stay focused during school.

3. What impact does the disease have on family or caregivers?

As a mother, I am continuously worried about my son's physical and mental health. I worry my son was left behind at recess again because he cannot keep up with the other children. I worry about how he carries his hot lunch. I worry about him navigating field trips and Halloween parades at the school. I worry about him breaking a bone, which could mean he may never walk again.

Aside from the worry, my husband and I have taken off several days from work to attend doctor appointments and school functions so that our son can participate as normally as possible in activities like field days, classroom parties, school fundraisers etc.

There are many costs associated with a disability, which is emotionally and financially stressful. Whether it be paying for new equipment, doctor visits, therapy visits, getting an adaptive bike, building or buying an accessible home and vehicle.

4. What else should ICER know about living with the disease or condition (e.g. impact on your ability to work, exercise, care for family, etc.)?

There are many things we take for granted like being able to participate in the same activities as others, choosing any seat at a sporting event or concert, taking a hike, or even wearing snow boots (our son cannot wear many snow boots because they are too heavy for him). Logistics and accessibility are always in the forefront of our mind when planning anything whether it be a family vacation, play date or field trip.

5. What outcomes are most important to patients? For example, is the top priority improved quality of life, longer survival, or relief of a specific symptom?

Improving or maintaining any strength...no matter how little it may seem. Because until you live with SMA, you do not realize how every little bit of strength maintained or gained helps to improve the quality of life.

6. Are there new/emerging treatments that the patient community is anticipating? What are the benefits or disadvantages of the new treatments (e.g. more or fewer side effects, convenience, effectiveness, etc.)? Do you think the benefits will outweigh side effects or risks?

My son is on a relatively new treatment (Spinraza) that requires an intrathecal administration of the drug. The benefits my son receives from this treatment outweighs the short-term effects he experiences. Because Spinraza is a relatively new drug, the long-term side effects are unknown however; it is a risk we are willing to take for the sake of our son's quality of life.

There are a few additional drugs in the pipeline that look promising for SMA patients however I do not have enough information to comment more on them.

7. Do patients have trouble getting insurance coverage for treatment? Do costs affect patients' choice of treatment, or their ability to access treatment?

Getting approval for Spinraza has been a painfully slow process for many however, we were fortunate to get approval from our insurance relatively quickly.

8. Please share any other information that you think is important for us to know from a patient perspective.

Saving a life is as important as improving the quality of life – both are priceless. It is also essential that each person be given the right to choose what is important to him or her with respect to treatment and treatment options.

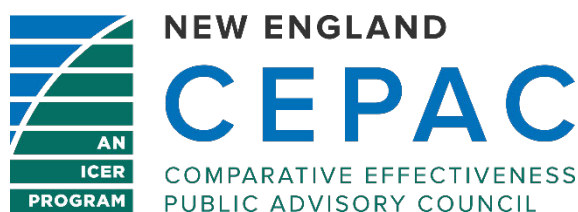


Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Evidence Report

February 22, 2019

Prepared for



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Alexandra Ellis served as the lead author for the report and wrote the background, other benefits, and contextual considerations sections of the report. Kristin Mickle led the systematic review and authorship of the comparative clinical effectiveness section with the support of Serina Herron-Smith. Varun Kumar was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Laura Cianciolo authored the section on coverage policies and clinical guidelines. Matt Seidner provided editorial feedback. Praveen Thokala and Matt Stevenson developed the cost-effectiveness model and authored the corresponding sections of the report. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Rick Chapman and Milon Watthuhewa for their contributions to this report. The modeling group would also like to thank Kate Ren for advice on survival modeling.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at <http://www.icer-review.org>.

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The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC Council is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about the New England CEPAC is available at <https://icer-review.org/programs/new-england-cepac/>.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER’s researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. This individual should not be considered responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

*For a complete list of stakeholders from whom we requested input, please visit:
<https://icer-review.org/material/sma-stakeholder-list/>*

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No relevant conflicts of interest to disclose, defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table of Contents

Executive Summary.....	ES1
1. Introduction	1
1.1 Background	1
1.2 Scope of the Assessment	4
1.3 Definitions.....	8
1.4 Insights Gained from Discussions with Patients and Patient Groups.....	10
1.5 Research, Development, and Manufacturing Costs	11
1.6. Potential Cost-Saving Measures in SMA	11
2. Summary of Coverage Policies and Clinical Guidelines	12
2.1 Coverage Policies	12
2.2 Clinical Guidelines	14
3. Comparative Clinical Effectiveness	16
3.1 Overview	16
3.2 Methods	16
3.3 Results	19
Infantile-Onset (Type I) SMA.....	20
Later-Onset (Type II and III) SMA.....	32
Presymptomatic SMA	38
All Populations: Harms.....	40
3.4 Controversies and Uncertainties	43
3.5 Summary and Comment	44
4. Long-Term Cost Effectiveness.....	49
4.1 Overview	49
4.2 Methods.....	49
4.3. Results.....	66
4.4 Summary and Comment	90
5. Potential Other Benefits and Contextual Considerations.....	93
6. Value-Based Price Benchmarks.....	95
7. Potential Budget Impact	97

7.1 Overview	97
7.2 Methods	97
7.3 Results	98
References	101
Appendix A. Search Strategies and Results.....	109
Appendix B. Previous Systematic Reviews and Technology Assessments	114
Appendix C. Ongoing Studies.....	115
Appendix D. Comparative Clinical Effectiveness Supplemental Information.....	125
Appendix E. Comparative Value Supplemental Information.....	158
Appendix F. Supportive Care Clinical Guidelines	196

List of Acronyms Used in this Report

AAN	American Academy of Neurology
AAV9	Adeno-associated virus serotype 9
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
CADTH	Canadian Agency for Drugs and Technologies in Health
CHOP-INTEND	Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMS	Centers for Medicare and Medicaid Services
EAP	Expanded access program
FDA	Food and Drug Administration
GDP	Gross domestic product
GMFM	Gross Motor Function Measure
HINE	Hammersmith Infant Neurological Examination
HFMSE	Hammersmith Functional Motor Scale-Expanded
LCD	Local Coverage Determination
LY	Life year
NCD	National Coverage Determination
NICE	National Institute for Health and Care Excellence
PSA	Probabilistic sensitivity analysis
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RULM	Revised Upper Limb Module
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
UHC	UnitedHealthcare
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WHO	World Health Organization
WTP	Willingness-to-pay
6MWT	6-minute walk test

Executive Summary

Background

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children.^{1,2} In the United States (US), SMA incidence is approximately one in 10,000 live births or about 500 new SMA cases per year.³ The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.⁴⁻⁶ *SMN1* creates SMN protein, a protein essential for motor neuron development. Although the survival motor neuron 2 (*SMN2*) gene also produces SMN protein, only a small amount of the protein it creates is functional. Hence, while the number of *SMN2* copies modulates the severity of SMA, patients without *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.⁷ This deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor functions.¹

SMA subtypes are related to age of onset and number of motor milestones achieved (see Table ES1 below).^{2,8} Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Type I SMA (infantile-onset SMA) represents approximately 60% of all diagnosed SMA cases.³ Approximately 20-30% of patients diagnosed with SMA have Type II and approximately 10-20% have Type III.^{2,3} Type IV SMA, a very rare and the least severe subtype, presents in adults.

Table ES1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of <i>SMN2</i> Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.²

Number of *SMN2* copies based on Calucho et al. 2018.⁹

Historically, life expectancy in the most common and severe form of SMA (Type I) was less than two years. Survival depends on respiratory function, and many infants and children eventually require permanent ventilation. SMA does not affect cognitive function, and there is often a contrast between a patient's alertness and ability to move. To maintain mobility and function as long as possible, multidisciplinary, supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.¹⁰⁻¹² Nevertheless, supportive care does not modify disease progression and patients may be entirely dependent on family members and caregivers.

The intense care and physical effort involved with caring for a patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.^{13,14} Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Diagnosis of SMA is typically prompted by the clinical symptoms of muscle weakness, and because of SMA's rapid progression, early treatment to preserve motor functioning is important. Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.¹⁵ Spinraza, an antisense oligonucleotide, targets *SMN2* so that it creates more functional SMN protein. It is administered via intrathecal injection (into the fluid surrounding the spinal cord) with four loading doses (day 0, day 14, day 28, and day 63) and maintenance doses every four months thereafter. Spinraza has been studied in patients with or likely to develop SMA Types I-III,¹⁶⁻¹⁸ with several studies ongoing.¹⁹⁻²¹ In December 2016, the Food and Drug Administration (FDA) approved Spinraza for the treatment of SMA (any subtype).¹⁵

A new gene therapy, Zolgensma® (onasemnogene abeparvovec, Novartis/AveXis), is currently in development to treat patients with SMA. Zolgensma, formerly known as AVXS-101, uses the adeno-associated virus serotype 9 vector to deliver a copy of *SMN* to supplement the defective *SMN1*.²² Zolgensma is being studied as a one-time, intravenous administration. The FDA granted Zolgensma a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected by mid-2019.²³

In this report, we review the clinical evidence on both drugs and estimate their long-term cost-effectiveness and potential budget impact.

Insights Gained from Discussions with Patients and Patient Groups

Throughout the conceptualization of this review, we heard from patient advocates and caregivers how devastating the diagnosis of Type I SMA can be and how difficult it is to watch the disease progress in a child. Parents and caregivers feel helpless and fearful while also needing to be vigilant and constantly providing care. Care entails approaches to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. We heard from adults with SMA how frustrating it is that new interventions have not been commonly studied in adults and that more data are needed in this population, including data on appropriate dosages. Patients and caregivers reported wanting treatments that improve strength and the ability to live more independently. We also heard extensively about the importance of early identification of and treatment for SMA. In addition, six families submitted public comments on our [Draft Scope](#), which provided additional context on the experience of children with SMA and their parents. These comments described the devastating urgency of treatment and severity of SMA symptoms, and many described the positive impact of treatment.

To supplement our discussions and open input comments, we also reviewed the “Voice of the Patient” report, which summarizes a Patient-Focused Drug Development meeting hosted by Cure SMA in April 2017.²⁴ The meeting gathered patients' and families' perspectives on living with SMA and on current and future therapies. Many of the key themes from the meeting echoed those we heard from our conversations with caregivers and patient advocates. Additional themes related to burden of disease included communication challenges as children with SMA grow, the concern of developing scoliosis (particularly for patients with Type II), and the constant worry about further loss of functional ability. Additional themes related to treatment options included optimism about disease modifying treatments, an expectation that some symptoms will exist even with treatment, and a desire for treatments that improve strength and functional ability while also valuing treatments that stabilize the disease.

Following our scoping discussions and public comment periods, we updated our draft scope to include efficacy outcomes related to bulbar function (e.g., swallowing, speaking) to better reflect what is important to patients with SMA and their families. These families' experiences provided patient-centered context for interpreting clinical trial outcomes by communicating the importance of independent functioning for older children and adults with SMA, and delay of disease progression for infants and younger children with SMA. These comments particularly underscored the importance of not only improved mobility, but also slowed progression and stabilization of current motor functions including smiling and independent sitting, eating or feeding, toileting, and transferring from wheelchairs.

ICER also received public comments on its [Draft Evidence Report](#) from a mix of patients, patient advocacy organizations, manufacturers, and providers. All three families who provided public comments described children with SMA who are receiving Spinraza; these families all reported a positive outlook on treatment with Spinraza. We also heard from three patient advocacy organizations who provided context about the patient experience living with SMA as well as feedback on key decisions made in the cost-effectiveness evaluation. We also heard from patients at different time points in this review about the spillover effects of this disorder on patients' caregivers, mainly parents, and we explored approaches to incorporate this caregiver burden into our model accordingly. However, due to the methodological uncertainty in estimating caregiver quality of life over a long-term horizon, we did not include this in our analyses. Further details are provided in Section 4.

Potential Cost-Saving Measures in SMA

Stakeholders did not identify any opportunities to reduce unnecessary care or other cost-saving measures in the care of SMA that could help provide resources for new treatments.

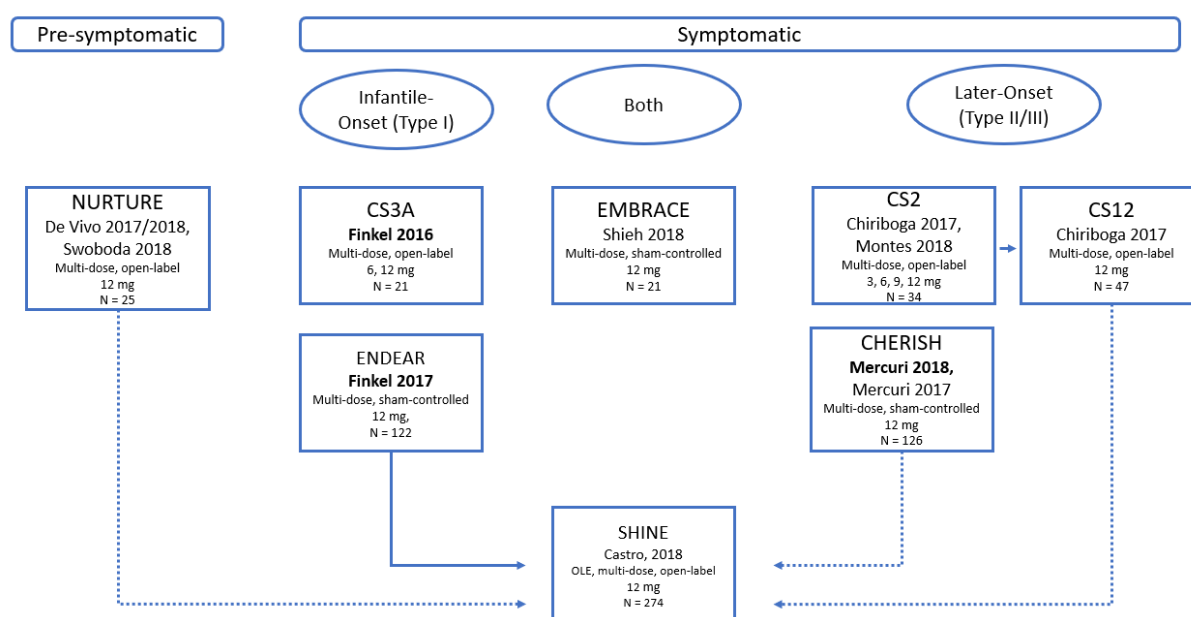
Comparative Clinical Effectiveness

This review focused on efficacy, safety, and effectiveness of Spinraza and Zolgensma in comparison to supportive care (with or without sham administration) in SMA patients of all ages and types.

Below, we summarize the evidence on the following key outcomes: mortality, permanent ventilation, motor function and milestones, and safety.

Spinraza clinical trials include: one randomized controlled trial (RCT) with a sham control (ENDEAR) and one open-label, dose-escalation study (CS3A) in Type I SMA; one RCT with a sham control (CHERISH) and one open-label, multiple dose study (CS2/CS12) in Type II/III SMA; one open-label, single-arm study (NURTURE) in presymptomatic SMA; and one RCT with a sham control (EMBRACE) in patients with Type I, II, or III SMA ineligible for the other trials (Figure ES1). Patients who completed the above trials were eligible to enroll in a single-arm, open-label extension (OLE) study (SHINE). Note that for SHINE, results are currently available for only the patients with Type I SMA who had been enrolled in ENDEAR.

Figure ES1. Clinical Trials of Spinraza



Results are not yet available for the individuals who enrolled in SHINE from the trials indicated with dashed lines.

In addition, we identified three cohort studies of patients with Type I SMA receiving Spinraza through extended access programs and two cohort studies in patients with Type II SMA receiving Spinraza. Details of these studies are described in Section 3 of this report.

The evidence base for Zolgensma consists of one open-label, two-cohort clinical trial (CL-101) in patients with infantile-onset (Type I) SMA and its extension study (START).²² Note that in CL-101,

three infants received a low-dose of Zolgensma and 12 infants received a high-dose of Zolgensma. This Executive Summary focuses on the high-dose cohort only; results from the low-dose cohort are described in Section 3.

We did not identify any studies of patients with Type 0 or Type IV SMA. Below, we summarize the evidence on clinical benefits by type of SMA (infantile-onset, later-onset, presymptomatic). Harms are summarized together for all populations.

Infantile-Onset (Type I) SMA: Clinical Benefits

Evidence Base for Spinraza

We included three clinical trials of Spinraza in infantile-onset (Type I) SMA, including two RCTs with sham control (ENDEAR and EMBRACE)^{17,25} and one open-label, dose-escalation study (CS3A).¹⁶ Longer-term results are also available for infants in ENDEAR who enrolled in the single-arm OLE (SHINE).²⁶

Note that for ENDEAR, an interim analysis comparing the proportion of Hammersmith Infant Neurological Examination-Section 2 (HINE-2) responders was completed when 78 patients were followed for at least six months (“interim efficacy set”: 27 sham control and 51 Spinraza patients; 43 patients were not yet followed for six months).¹⁷ This analysis showed statistical superiority of HINE-2 responders favoring Spinraza and the study was subsequently terminated prior to the planned 13-month follow up. Because of the early termination, there are differences in the number of infants included in the outcomes assessed as noted in the results below.

EMBRACE enrolled infants and children with Type I, II, or III SMA who were ineligible for other Spinraza trials. In this section, we only report on the subgroup of infants with Type I SMA. Results for the subgroup of children with Type II/III SMA are presented in the subsequent section.

Evidence Base for Zolgensma

We included one open-label, two-cohort clinical trial of Zolgensma (CL-101) and its extension study (START) in infantile-onset (Type I) SMA.²² Below, we present results from the 12 infants in the high-dose cohort.

Baseline Characteristics of Key Trials

Key baseline characteristics of the two key trials (ENDEAR for Spinraza and CL-101 for Zolgensma) are shown in Table ES2. Infants in both trials had two copies of *SMN2*. Note that infants in ENDEAR were diagnosed and treated later, on average, than those in CL-101. Given these differences, direct comparisons between the trials’ results should not be made.

Table ES2. Key Baseline Characteristics of ENDEAR and CL-101

Key Characteristics	ENDEAR ¹⁷		CL-101 ²²
	Spinraza	Sham Control	Zolgensma
No. of Participants	80	41	12
Age at Onset, months	1.8 (0.5-4.2)*	2.2 (0.2-4.6)*	1.4 (0-3.0)
Age at Diagnosis, weeks	12.6 (0-29)	17.5 (2-30)	8.6 (0-19.4)†
Disease Duration, weeks	13.2 (0-25.9)	13.9 (0-23.1)	NR
Age at Treatment Initiation, months	5.4 (1.7-8.0)‡	6.0 (1.0-8.6)‡	3.4 (0.9-7.9)
Ventilatory Support, n (%)	21 (26)	6 (15)	2 (17)
Nutritional Support, n (%)	7 (9)	5 (12)	5 (42)
Mean HINE-2 Score	1.29 ± 1.07	1.54 ± 1.29	ND
Mean CHOP-INTEND Score	26.63 ± 8.13	28.43 ± 7.56	28 (12-50)

Data are mean (range) or ±SD.

CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, HINE-2:

Hammersmith Infant Neurological Examination-Section 2, ND: no data, NR: not reported

*Converted from weeks to months by multiplying by 12 months and dividing by 52 weeks.

†Converted from days to weeks by dividing value by 7.

‡Converted from days to months by multiplying by 12 months and dividing by 365 days.

Clinical Benefits: Survival and Permanent Ventilatory Support

In ENDEAR, permanent ventilatory support was defined as ventilatory support or tracheostomy for at least 16 hours per day for 21 days without an acute, reversible event. Spinraza demonstrated a statistically-significant 47% decrease in the risk of death or permanent assisted ventilation compared with sham (HR [95% CI]: 0.53 [0.32, 0.89], $p=0.005$); 31/80 (39%) of Spinraza and 28/41 (68%) of sham control recipients died or needed permanent ventilatory support.¹⁷ In the sham control group, the median time to death or permanent assisted ventilation was 22.6 weeks, whereas the Spinraza group had not reached this endpoint by the end of the trial. Interim long-term follow-up data from SHINE show the median time to death or permanent ventilation for infants who received Spinraza in ENDEAR and SHINE was 73.0 weeks (95% CI: 36.3, NA).²⁶

Seven infants receiving Spinraza in the CS3A study died or required permanent ventilation; because most infants in CS3A were alive and without permanent ventilation, the median age of event-free survival was not reached.¹⁶

In CL-101, permanent ventilatory support was defined as ventilatory assistance for at least 16 hours per day for at least 14 days without an acute, reversible illness. All infants treated with Zolgensma in CL-101 were alive and event-free through 24 months of follow-up.^{22,27} One patient in the low-dose cohort met criteria for permanent ventilatory support but later improved; this patient was considered event-free.

Clinical Benefits: Hammersmith Infant Neurological Examination-Section 2 (HINE-2)

HINE-2 scores or response were reported in three trials of Spinraza (ENDEAR, EMBRACE, CS3A), but this outcome was not measured in the Zolgensma study. HINE-2 consists of eight items to assess infants' changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Partial attainment of a skill can be captured in subscores. Each milestone is measured on a 3- to 5-point scale with higher scores indicating better functioning. To meet responder criteria, infants had to improve in one or more milestones and show more milestones with improvement than worsening. In ENDEAR, the mean HINE-2 score in infants receiving Spinraza improved over the course of treatment whereas the mean HINE-2 score in infants receiving sham did not improve. In ENDEAR and EMBRACE, high proportions of HINE-2 responders were reported among patients with Type I SMA receiving Spinraza; no one who received sham met responder criteria (Table ES3). In addition, 13 of 15 (87%) children with Type I SMA receiving Spinraza in the CS3A study met identical criteria as HINE-2 responders.¹⁶

Table ES3. HINE-2 Results for Spinraza in Infantile-Onset (Type I) SMA

	ENDEAR ¹⁷		EMBRACE ²⁸	
Treatment	Spinraza	Sham Control	Spinraza	Sham Control
Assessment Timepoint	Day 183*		14 months	
No. of Participants	59	23	9	4
Mean Baseline Score, Points	1.29 ± 1.07	1.54 ± 1.29	NR	NR
Mean Change from Baseline, Points	2.4 (2.8, 3.1)	0 (-0.3, 0.3)	NR	NR
Responder†‡, n (%)	21 (41)‡	0‡	7 (78)	0

Data are mean (min, max) or ±SD.

HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported

*Data estimated from publication by ICER.

†Responder defined as meeting two criteria: score improvement in one or more categories and improvement in more motor milestone categories than worsening.

‡Based on interim data analysis. Denominators were 51 for Spinraza and 27 for sham control.

Clinical Benefits: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

CHOP-INTEND results were reported in two trials of Spinraza (ENDEAR, CS3A) and in the CL-101 study of Zolgensma. CHOP-INTEND assesses 16 motor skills, and each motor skill is scored from 0 (no response) to 4 (complete response). On average, healthy infants aged three months have a CHOP-INTEND score (range) of 50.1 (32-62) while similarly-aged infants with SMA have an average score of 20.2 (10-33) points.²⁹ The literature typically cites a 40-point threshold as indicating clinically-meaningful function; it is rare for infants with Type I SMA to ever achieve a score of 40 or more points on the CHOP-INTEND.^{30,31} A 4-point change is generally considered an important

change in CHOP-INTEND response. Overall, improvements in CHOP-INTEND scores were observed among infants receiving Spinraza or Zolgensma (Table ES4).

Table ES4. CHOP-INTEND Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR ¹⁷		CS3A ¹⁶	CL-101 ²²
Follow-Up	Final analysis*		18 months	Interim analysis†
Treatment	Spinraza	Sham control	Spinraza	Zolgensma
No. of Participants	73	37	14	12
Mean Baseline Score, Points	26.63 ± 8.13	28.43 ± 7.56	30 (17-64)	28.2 (12-50)
Mean Change from Baseline, Points	NR	NR	15.2	24.6
Responder‡, n (%)	52 (71)	1 (3)	12 (86)	NR

Data are mean (range) or ±SD. Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table ES3.

CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, NR: not reported

*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.

†Data cut-off at August 7, 2017. 7/12 patients had 24 months of follow-up.

‡Responder defined as achieving ≥4-point increase in CHOP-INTEND score.

Clinical Benefits: Specific Motor Milestones

Motor milestones achieved among infants treated with Spinraza (ENDEAR) and Zolgensma (CL-101) are shown below in Table ES5. Among infants with at least six months of follow-up in ENDEAR, no infant who received sham achieved any milestone, whereas 22% of patients who received Spinraza achieved head control and 1% achieved standing with assistance. Long-term follow-up data shows additional motor milestone achievements for infants receiving Spinraza who transitioned from ENDEAR to SHINE. Data from the interim analysis (June 15, 2017) are presented in Table ES6.²⁶ After 576 days, approximately 45% of infants achieved full head control and 29% achieved sitting independently.

Table ES5. Motor Milestone Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

Other Motor Milestones	ENDEAR ^{17*}		CL-101 ^{22†}
	Spinraza N=73	Sham Control N=37	Zolgensma N=12
Head Control	16 (22)	0	11 (92)
Roll Over	7 (10)	0	9 (75)
Sitting Unassisted	6 (8)‡	0‡	10 (83) [§]
Standing with Assistance	1 (1)	0	2 (17)
Standing Independently	NR	NR	2 (17)
Walking Independently	NR	NR	2 (17)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table ES3.

HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported

*The HINE-2 motor milestone achievements of infants at the later of days 183, 302, and 394. Infants with opportunity for at least a 6-month assessment were included.

†24 month follow-up.

‡Includes “stable sit” and “pivots” from HINE-2.

§Sitting unassisted for at least 10 seconds is in accordance with WHO Motor Milestones criteria.

Table ES6. ENDEAR to SHINE Motor Milestone Achievements in Infantile-Onset (Type I) SMA²⁶

	Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
No. with Available Data	81	70	65	51	48	31	17
% Achieved Full Head Control	0	7	17	25	33	45	35
% Achieved Independent Sitting	0	1	5	10	15	29	24

Data are from children who received Spinraza in ENDEAR and SHINE.

After 24 months since Zolgensma treatment, 92% of patients achieved head control and 17% could walk independently (Table ES5). Two more children achieved standing with support during additional follow-up in START.³²

Later-Onset (Type II/III) SMA: Clinical Benefits

Evidence Base for Spinraza

One RCT with sham control (CHERISH) reported on outcomes of Spinraza in children ages two to 12 years with later-onset SMA (Types II or III), and one Phase Ib/IIa open-label, multiple dose study (CS2/CS12) reported on outcomes in children ages two through 15 with later-onset SMA.^{18,28} In addition, the sham-controlled EMBRACE trial, which included children with Type I, II, or III, presented results on the subgroup of eight children diagnosed with later-onset (Type II/III) SMA, with broader inclusion criteria than that of CHERISH.

Note that for CHERISH, the sponsor conducted a prespecified interim analysis of the primary outcome (Hammersmith Functional Motor Scale-Expanded; HFMSE) when all children had been enrolled for a minimum of six months **and** 39 or more children had completed 15-month evaluations.¹⁷ Results of the interim analysis showed a statistically-significant benefit on HFMSE score favoring Spinraza, and CHERISH was terminated early.

Evidence Base for Zolgensma

We did not identify any trials assessing Zolgensma in this population.

Clinical Benefits: Survival and Permanent Ventilatory Support

There were no deaths during CHERISH or CS2/CS12, and no data on permanent ventilation were available.

Clinical Benefits: Hammersmith Functional Motor Scale-Expanded (HFMSE)

HFMSE was reported in CHERISH and CS2/CS12.^{18,28} The HFMSE is a clinician-rated, 33-item scale developed to assess the motor ability of children with SMA with limited ambulation. Each item in the HFMSE is measured on a 3-point scale with higher scores indicating better functioning. Untreated patients with SMA Type II or III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.^{33,34}

The interim analysis of CHERISH included 15-month data from 39 Spinraza and 19 sham control recipients, which is 43% of the enrolled population; authors imputed data for the remaining 45 Spinraza and 23 sham control recipients. At the interim analysis, Spinraza demonstrated a statistically-superior least-squares mean increase from baseline HFMSE score compared to the sham control (Table ES7), leading to early study termination.¹⁸ For the final analysis, HFMSE data from 18 Spinraza and eight sham control recipients were imputed, as these children still had not yet completed the 15-month assessment. With fewer data imputed, results from the final analysis of mean increase from baseline HFMSE showed a smaller treatment difference than from the interim analysis, although the results remained favorable to Spinraza (mean difference [95% CI]: 4.9 [3.1, 6.7], Table ES7).¹⁸ A greater proportion of children who received Spinraza showed a response of ≥ 3 -point increase in HFMSE score versus the sham control, and the calculated odds ratio favored Spinraza treatment over sham control (odds ratio [OR] [95% CI]: 6 [2-15]).

At study day 253 in CS2/CS12, 9/11 (82%) and 3/16 (19%) SMA Type II and III children improved by ≥ 3 points from baseline HFMSE.²⁸

Table ES7. HFMSE Results from CHERISH in Later-Onset (Type II/III) SMA

CHERISH ¹⁸			
	Spinraza* N=84	Sham Control* N=42	Treatment Difference†
Interim Analysis			
n (%) with 15-Month Data	35 (42)	19 (45)	--
n (%) with HMFSE Data Imputed	49 (58)	23 (55)	--
HFMSE‡ Change from Baseline	4.0 (2.9-5.1)	-1.9 (-3.8-0)	5.9 (3.7, 8.1)
Final Analysis			
n (%) with 15-Month Data	66 (79)	34 (81)	--
n (%) with HMFSE Data Imputed	18 (21)	8 (19)	--
HFMSE‡ Change from Baseline	3.9 (3.0-4.9)	-1.0 (-2.5-5.0)	4.9 (3.1, 6.7)
% of HFMSE Responders§	57 (46-68)	26 (12-40)	OR: 6 (2, 15)

HFMSE: Hammersmith Functional Motor Scale-Expanded, OR: odds ratio

*Data are mean (min-max) or n (%).

†Data are the difference in treatment with Spinraza vs. sham (95% CI).

‡Least-squares mean change from baseline.

§Defined as change from baseline of ≥3 points.

Clinical Benefits: Upper Limb Function

Revised Upper Limb Module (RULM) is an assessment of 19 tasks designed to assess upper limb function in non-ambulatory patients with SMA. Each item is measured on a 3-point scale with higher scores indicating better functioning.³⁵ In CHERISH, upper limb motor function measured via RULM improved with Spinraza treatment (least-squares mean score [95% CI]: 4.2 [3.4, 5.0]) and remained stable in the sham control group (0.5 [-0.6, 1.6]). The treatment difference for RULM score (3.7 [2.3, 5.0]) was not formally tested for statistical significance.

In CS2/CS12, four of six (67%) children with Type II SMA followed through day 1,050 demonstrated clinically-meaningful improvement (≥2 points) in upper limb motor function, as assessed by ULM. Motor function of all children (n=6) with Type III improved, based on the clinically-meaningful threshold for the 6-minute walk test (6MWT; gain of ≥30 meters).

Clinical Benefits: Specific Motor Milestones

New achievements in walking with assistance, standing alone, and any World Health Organization (WHO) motor milestone in children with later-onset SMA were reported by similar proportions of Spinraza and sham control groups in CHERISH (Table ES8). Note these data were analyzed only among the children who had completed the 15-month assessment (i.e., no data were imputed). One child in each group gained the ability to stand alone, and one child in the Spinraza group achieved walking with assistance.¹⁸ Of the eight children in EMBRACE with later-onset SMA, 2/5

(40%) of those who received Spinraza and 2/3 (66%) of those who received sham achieved standing (Table ES8).

Table ES8. Motor Milestone Results for Spinraza in Later-Onset (Type II/III) SMA

	CHERISH ¹⁸		EMBRACE ³⁶	
	Spinraza* N=84	Sham Control* N=42	Spinraza N=5	Sham Control N=3
Assessment Timepoint	Final Analysis		Final Analysis†	
N (%) Analyzed	66 (79)	34 (81)	5 (100)	3 (100)
% Who Achieved New WHO Motor Milestone	20 (11-31)	6 (1-20)	NR	NR
Sitting, n (%)	NR	NR	4 (80)	1 (33)
Crawling, n (%)	NR	NR	3 (60)	1 (33)
Standing, n (%)	1 (2)‡	1 (3)‡	2 (40)§	2 (67)§
Walking, n (%)	1 (2)‡	0 (0)‡	1 (20)§	0§

NR: not reported, WHO: World Health Organization

*Data are mean (min-max) or n (%).

†Individuals with 6 month (day 183), 10 month (day 304), and 14 month (day 422) visit included. The last assessment available was used for this analysis.

‡Per WHO motor development milestones definition.

§Per HINE-2 definition.

Presymptomatic SMA: Clinical Benefits

Evidence Base for Spinraza

One ongoing, single-arm study (NURTURE) reported on Spinraza treatment in 25 presymptomatic infants with two or three copies of *SMN2*. Number of copies of *SMN2* is predictive of SMA type, with infants with two copies more likely to have Type I SMA and those with three copies more likely to have Type II/III SMA. In NURTURE, the most recent interim analysis was completed in May 2018, at which time the median age was 26.0 months (range: 14.3-34.3), and median time on treatment was 27.1 months (15.1-35.5).

Evidence Base for Zolgensma

Trials of Zolgensma are ongoing and no data have been presented to date.

Clinical Benefits: Survival and Permanent Ventilatory Support

As of May 2018, all 25 children were alive and no children required permanent ventilatory support. Four (16%) children met the primary outcome of required respiratory intervention (defined as requiring six or more hours per day for seven consecutive days or tracheostomy); all four children

had two *SMN2* copies. All of these children received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy.

Clinical Benefits: CHOP-INTEND

With a median (range) time on treatment of 27.1 months (15.1-35.5), the mean (range) CHOP-INTEND scores for children with two and three *SMN2* copies were similar and reflected near-maximal motor function (two copies: 61.0 [46-64]; three copies: 62.6 [8-64]).

Clinical Benefits: Specific Motor Milestones

By May 2018, caregivers reported all 25 (100%) children had achieved sitting without support, 22/25 (88%) of children had achieved walking with assistance, and 17/25 (68%) had achieved walking alone (Table ES9).

Table ES9. WHO Motor Milestone Achievements for Spinraza in Presymptomatic SMA

WHO Motor Milestone	Expected Age Range of Attainment*	July 2017†‡		May 2018†§	
		2 <i>SMN2</i> Copies	3 <i>SMN2</i> Copies	2 <i>SMN2</i> Copies	3 <i>SMN2</i> Copies
Independent Sitting	3.8 – 9.2	14 (93)	8 (80)	15 (100)	10 (100)
Walking with Assistance	5.9 – 13.7	5 (33)	7 (70)	12 (80)	10 (100)
Walking Alone	8.2 -17.6	3 (20)	5 (50)	8 (53)	9 (90)

*Data reported in months. Range defined by 1st-99th percentile for the windows of milestone achievement.

†Data reported as N (%).

‡The median age at the most recent visit was 14.7 months (range: 2.8-23.3).

§The median age at the most recent visit was 26.0 months (range: 14.3-34.3).

All Populations: Harms

Safety data were collected in four clinical trials of Spinraza (ENDEAR, CHERISH, EMBRACE, and SHINE) and in the trial of Zolgensma (CL-101).

Harms with Spinraza

Sixteen percent of infants who received Spinraza and 39% of sham control infants in ENDEAR discontinued study participation due to adverse events (AEs).¹⁷ No children in CHERISH or NURTURE discontinued due to AEs.^{18,37}

Treatment-related AEs were rare in all Spinraza trials. Serious AEs were more frequently reported by sham control than Spinraza recipients in ENDEAR (95% vs. 76%, respectively) and CHERISH (29% vs. 17%, respectively).^{17,18} Many of the frequently-reported AEs reported following treatment with Spinraza were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain). Lumbar-puncture-associated AEs were reported only by children in CHERISH; however, this is

likely due in part to the difficulty of collecting this information from infants. Additional common AEs associated with Spinraza include lower respiratory tract infection and constipation. Fever was more common among infants (ENDEAR) than older children (CHERISH) compared to the sham control.

Based on clinical trial data and known side-effects related to oligonucleotides with a phosphorothioate backbones,³⁸ two safety concerns are highlighted in the Spinraza prescribing information: risk of thrombocytopenia and potential for kidney damage (renal toxicity).¹⁵ FDA-required monitoring to assess patient safety includes coagulation and quantitative spot urine testing prior to each dose.

Harms with Zolgensma

In CL-101, two infants had elevated serum aminotransferase levels after Zolgensma infusion; both were considered treatment related and met criteria for grade 4 AEs.²² A protocol amendment requiring oral prednisolone treatment (1 mg/kg) for 30 days starting 24 hours prior to Zolgensma infusion was added following the first infant's dosing and subsequent serum aminotransferase elevation. Two infants also experienced asymptomatic elevations in serum aminotransferase levels which were deemed nonserious, treatment-related AEs.

Controversies and Uncertainties

The currently available trials of Spinraza (SMA Types I-III) and Zolgensma (SMA Type I) show prolonged survival and improved motor function compared with historical controls or sham injections. However, there remain several important uncertainties. First, for both interventions, the narrow eligibility criteria of trials and the limited sample size (especially for Zolgensma) raises concerns about generalizability of results to the wider population of patients with SMA. The ineligible or otherwise unselected patients are likely more severely ill, experience different or additional comorbidities (e.g., scoliosis), or have a different genetic profile than those selected for the clinical trials.

In addition, there is a lack of data on the long-term safety and efficacy of both interventions. The currently-available data do not indicate diminishing benefit, which is promising. Nevertheless, because SMA is a rare disease and the trials have short-term follow-up, understanding the long-term effects of Spinraza or Zolgensma will take time. For Spinraza, there is uncertainty in the long-term effects of the repeated lumbar punctures in patients, particularly as they age or progress along the disease course. In terms of other safety concerns, the Spinraza prescribing information notes the risks of thrombocytopenia and renal toxicity. For Zolgensma, there is uncertainty in the duration of expression of the novel gene therapy which may provide life-long benefit to patients. On the other hand, if the expression wanes over time, the subsequent treatment pathway is unclear. If antibodies to AAV form, the patient would be unable to receive another dose of

Zolgensma. In terms of safety, liver toxicity was mitigated by amending the protocol to include an administration of prednisolone before and after Zolgensma infusion. It will be important to monitor liver functioning in patients treated with Zolgensma. Long-term extension studies may provide additional data, and these studies are ongoing.

For Zolgensma, an additional concern is the single-arm design and the small sample size. Comparisons with historical controls can exaggerate perceived treatment effects, particularly when standards of care improve over time or when there is a variable natural history,³⁹ which are both true of SMA. For example, in older natural history studies, approximately 68% of patients with Type I SMA died by two years of age. In part due to the improvements in and increased utilization of nutritional and respiratory support, more recent estimates of mortality are approximately 30% at two years of age with approximately half of survivors reliant on noninvasive ventilation. In the trial of Zolgensma, although all 12 patients in the high-dose cohort remained alive and not using permanent ventilation at two years, the outcomes that would have been observed had a concurrent control group been included are unknowable.

Given the differences in baseline characteristics between the trials of infantile-onset (Type I) SMA, comparisons between Zolgensma and Spinraza should be avoided. For example, there are differences in age at treatment initiation and duration of disease, which are known to be modifiers of treatment effect. In addition, the time point of analysis (median of approximately nine months in ENDEAR and 24 months in START) and approach for assessing motor milestones (HINE-2 vs. WHO) differs between the studies. There is also an open question regarding the use of combination or sequential therapy with Zolgensma and Spinraza. Some patients who received Zolgensma in START went on to take Spinraza after the trial, but the effects of combination or sequential therapies have not been well studied.

Finally, for presymptomatic patients, the current evidence base is limited. As newborn screening for SMA becomes more common, it is likely that patients will be treated soon, perhaps before developing symptoms. A single-arm, uncontrolled study of Spinraza is ongoing with preliminary results presented only in conference form. A single-arm study of Zolgensma has started, but no results have been presented to date. Presymptomatic treatment may provide more benefit to patients, although there remains uncertainties in the current evidence base.

Summary and Comment

SMA is a rare, genetic neuromuscular disease that causes irreversible motor neuron damage that prevents patients from gaining or retaining motor functions. Survival depends on respiratory function, and many infants and children become permanently ventilated. Considering that SMA is a rare disease, the existing evidence base contains many of the common limitations pervasive in rare disease areas, including a small patient population, clinical trial design challenges, and lack of long-term safety and efficacy data. Overall, where data were available, Spinraza and Zolgensma

demonstrated improvements in motor function, survival, and need for permanent ventilatory support. The current limitations of the clinical evidence for Spinraza and Zolgensma include study populations that limit the generalizability of clinical outcomes to SMA patients who differ from those included in the trials, limited long-term safety (e.g., repeated lumbar puncture procedures) and efficacy data (e.g., durability of novel gene therapy), and the uncontrolled, open-label design of the CL-101 trial of Zolgensma. Should additional data regarding treatment safety and efficacy become available, the conclusions of this report may require updating.

A comprehensive summary of evidence ratings for Spinraza and Zolgensma for each population defined are shown in Table ES10. Additional details are provided in Section 3.5.

Table ES10. Evidence Ratings for Spinraza and Zolgensma for SMA

Population	Spinraza	Zolgensma	Ability to Distinguish?
Type 0 SMA	I*	I*	I†
Infantile-Onset (Type I) SMA	A	A	I
Later-Onset (Type II and III) SMA	B+	I*	I†
Type IV SMA	I*	I*	I*
Presymptomatic SMA	B+	I*	I†

*No studies (e.g., RCTs, observational, etc.) identified.

†Comparison is based on lack of available evidence for Zolgensma.

Spinraza for Infantile-Onset SMA

Based on the evidence, Spinraza demonstrated statistically-significant reductions in the need for ventilatory support and improvements in survival. Spinraza was also superior to standard care in improving motor function and milestone achievement, as measured by the HINE-2 and CHOP-INTEND assessments.

We noted some differences between the Spinraza and sham control groups at baseline which suggests more severe symptoms in the Spinraza group. We also noted potentially limited generalizability, as Type I SMA patients with more severe disease were underrepresented in the trials and may not adequately reflect the “real-world” patient population.

Despite these limitations, we have high certainty that Spinraza provides a substantial net health benefit compared to standard care and rate the evidence as “superior” to standard care (A).

Zolgensma for Infantile-Onset SMA

All infants in the Phase I CL-101 trial were alive following at least 24 months of follow-up. Infants also showed gains in CHOP-INTEND motor milestones and most infants who received the proposed therapeutic dose (cohort two) achieved full head control and rolling over motor milestones.

Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as “superior” to standard care (A).

Zolgensma versus Spinraza for Infantile-Onset SMA

Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of Zolgensma versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I).

Spinraza for Later-Onset SMA

Based on the single randomized controlled trial of Spinraza in later-onset SMA patients (CHERISH), Spinraza demonstrated statistically-superior improvements in changes from baseline HFMSE, and in the proportion of HFMSE responders, versus the sham control.

Spinraza’s superiority in improving HFMSE was evident at the interim analysis, and the study was subsequently terminated early. The interim analysis imputed data from approximately 57% of the enrolled population that had not yet been observed for the full 15-month period. Nevertheless, the final analysis, with 79% (100/126) of patients having been observed for 15-months, continued to show superior benefits of Spinraza on HFMSE scores. Among the 100 patients with observed 15-month data, Spinraza was not superior, however, in improving WHO motor milestone achievements such as unassisted sitting, standing, or walking compared to the sham control.

Similar to ENDEAR, we noted potentially limited generalizability, in that the trial population may not reflect the all patients eligible for treatment. Another limitation is that survival, ventilation, and event-free survival were not evaluated in CHERISH. Finally, we did not find any data regarding long-term safety and durability of clinical benefit.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as “incremental or better” (B+).

Spinraza for Presymptomatic SMA

Evidence from the NURTURE trial shows all 25 infants enrolled were alive and four (16%) children met the primary outcome of required respiratory intervention, all of whom had two *SMN2* copies. CHOP-INTEND scores for children with two and three copies were similar and reflected near-maximal motor function. Many children with one year of follow-up, however, had developed one or more clinical symptoms of SMA; the severity of these symptoms are not reported. Furthermore, we found only grey literature (i.e., conference presentations), which have not been peer-reviewed.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as “incremental or better” (B+).

Comparison of Evidence Ratings for Spinraza and Zolgensma

With respect to the comparison of Spinraza and Zolgensma in infantile-onset (Type I) SMA, the evidence base for Spinraza includes multiple randomized placebo-controlled trials, while the evidence base for Zolgensma is primarily an uncontrolled study in 12 patients. Despite the clear differences in evidence bases, in the ICER rating system, we have rated both therapies as “superior” to standard care (A) for patients with infantile-onset SMA. This judgment reflects that while we have far greater uncertainties about the exact net benefits of Zolgensma than Spinraza, the magnitude of effect in these 12 patients was large enough to have high certainty that Zolgensma provides a substantial net health benefit compared with standard care. Additionally, for both therapies, even if efficacy were maintained only for the duration already observed in the studies evaluating them, we would still assign an “A” rating to the therapies. As stated in [ICER Evidence Rating Matrix: A User’s Guide](#), “We find it useful to consider that conceptual confidence intervals around a point estimate that do not extend beyond a single box of comparative net health benefit represent a ‘high’ level of certainty.” The ratings of “A” for both therapies should not be interpreted to mean that we are able to state that they have similar net benefits, or that we believe the studies within the evidence bases to be of equal quality. It should also not be interpreted to mean that we have similar “conceptual confidence intervals” around net benefits – we do not. Such conceptual confidence intervals are much wider around the net benefit of Zolgensma than Spinraza. However, in each case we judge that the conceptual confidence intervals do not extend below “substantial” net benefit compared with standard care.

Long-Term Cost Effectiveness

We developed three *de novo* economic models that evaluated the cost-effectiveness of Spinraza and Zolgensma, each compared to best supportive care (BSC), from a US health care sector perspective for patients with SMA, in alignment with ICER’s [Value Assessment Framework for Ultra Rare Diseases](#). The models included 1) one for symptomatic patients with infantile-onset (Type I) SMA; 2) one for symptomatic patients with later-onset (Type II/III) SMA; and 3) one for presymptomatic SMA patients. For each population, we estimated the lifetime costs, life years gained, and quality adjusted life years (QALYs) gained, discounted at 3% per annum, for Spinraza and BSC. We used these results to generate incremental cost per QALY gained and incremental cost per life-year gained, comparing Spinraza to BSC. We also estimated these outcomes for Zolgensma among patients with Type I SMA and compared the results of Zolgensma versus BSC. Several scenario analyses evaluated the impact of a different perspective including a modified societal perspective, alternative survival, cost, and utility assumptions. Although we present a scenario analysis that compares Zolgensma to Spinraza, we do not consider this a suitable base case for the purposes of determining long-term value for money or as the basis of a value-based price recommendation as Spinraza is relatively new and our analyses suggest it is not cost effective at usual thresholds.

Performing an analysis on the incremental cost per “equal value of life years gained” (evLYG) was explored for this report. ICER committed to complement its cost per QALY calculations with a cost per evLYG result in order to provide policymakers with a broader view of cost-effectiveness. This new outcome measure was introduced too late in the course of this current review to be able to work out the technical aspects adequately, and therefore the cost per LYG is used as a surrogate result. As with the cost per evLYG, the cost per LYG considers any extension of life at the same “weight” no matter what treatment is being evaluated.

The models were dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other interim motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were included at utility benefit with interventions. All three models used the same model structure, and contained two main components: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model (Figures ES2 and ES3). Data inputs for the short-term model for each intervention was derived from their respective clinical trials and used directly to elicit patient proportions in each health state at different time points in this model. There is no trial of Zolgensma versus BSC, so data from the BSC arm in ENDEAR was used to inform this comparison.²²

Figure ES2. Model Schematic for Patients with Infantile-Onset (Type I) SMA and Presymptomatic SMA Patients

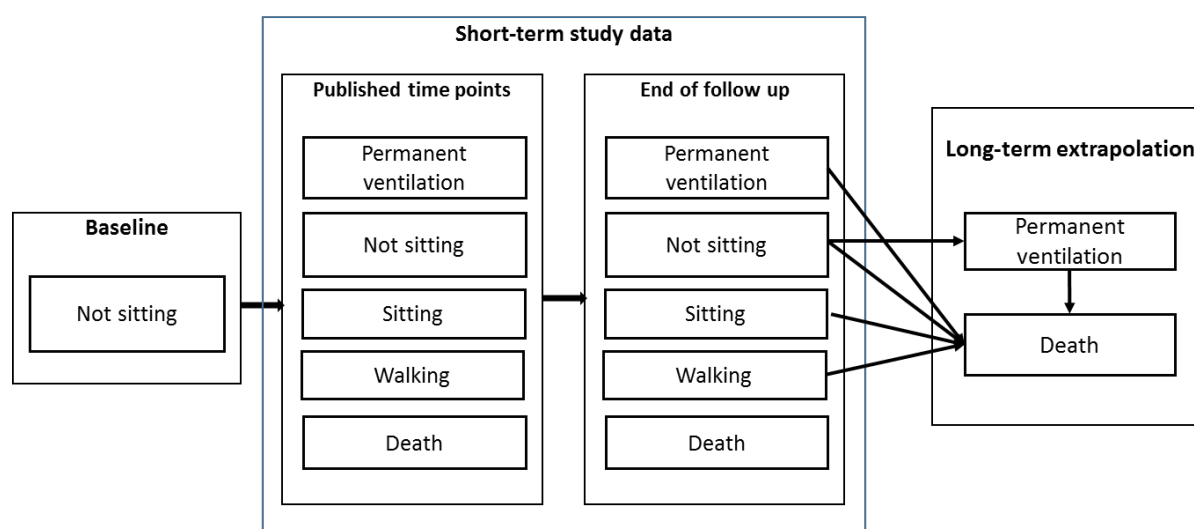
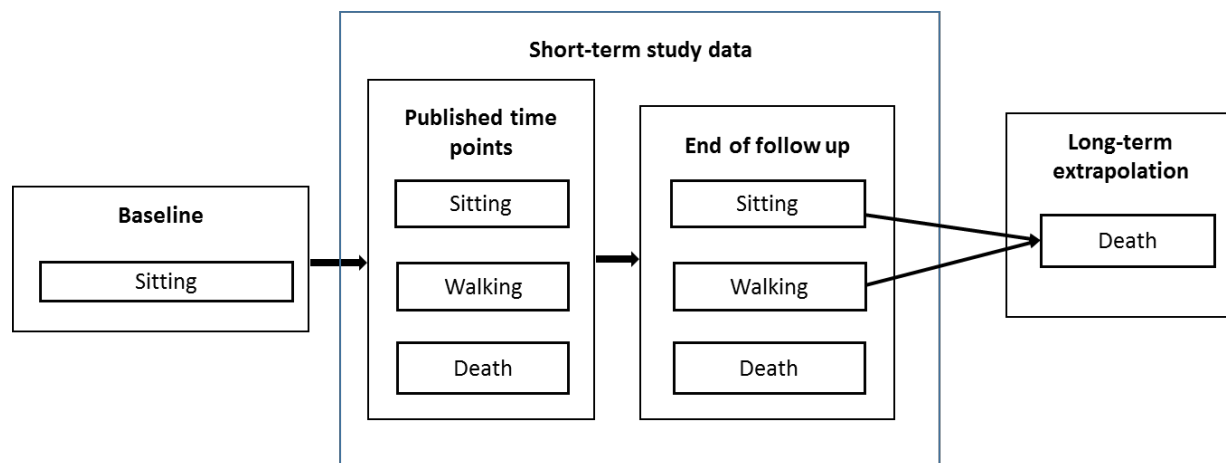


Figure ES3. Model Schematic for Patients with Later-Onset (Type II/III) SMA



The long-term model involved the extrapolation of motor function milestones, permanent ventilation, and mortality, the latter of which was assumed to be conditional on health states, over a lifetime horizon, using monthly (30.44 days) cycles. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death). In addition, we also modeled more conservative scenarios (only for Type I SMA patients) for the interventions where a proportion of patients lost milestones.

Our model was informed by several key assumptions listed below. A comprehensive list of assumptions and accompanying rationales for each assumption is available in Section 4 of the report.

- Our analyses used a naïve comparison between Zolgensma and BSC, and Spinraza and BSC due to non-availability of any published head-to-head trials comparing the two interventions to each other, or Zolgensma to any intervention.
- Data from the trials were used directly in the short-term model.
- In the short-term model for Spinraza, we assumed that the proportion of patients sitting among those alive who are not followed up is the same as the observed proportion of patients sitting among who attended the follow-up visits.
- Motor-function milestone achieved at the end of follow up were sustained until death.
- We assumed a utility benefit in the intervention arms for patients achieving interim motor function milestones such as head control, rolling, crawling, and standing. This was attributed to those patients in the “not sitting” and “sitting” health states.
- Only patients in the “not sitting” health state can transition to “permanent ventilation” state.

- Patients in the “not sitting” health state at the end of the short-term model had the same survival as those on “permanent ventilation.” This assumption is favorable to the drugs given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit.
- In the BSC arm, we used a partitioned survival approach to model at the end of the short-term model to estimate transitions to death and permanent ventilation from the “not sitting” health state. In the intervention arms we assumed the same mortality for those in the “not sitting” state as those in the “permanent ventilation” state.
- We assumed a treatment stopping rule at 24 months for patients on Spinraza who did not achieve motor function milestones with the treatment.

Model inputs pertaining to proportions in each health state vary by intervention and target population. As mentioned earlier, trial-specific inputs informed the short-term model directly, while the long-term model extrapolation was dependent on the health state patients were in at the end of the short-term model for each intervention. In the SMA Type I model, for Spinraza, data for the short-term model was derived from the ENDEAR and SHINE trials.^{22,26} The true proportion of patients on Spinraza who achieved motor-function milestones was derived using a multi-stage process which is described in more detail in Appendix Table E2. No patient in the BSC arm achieved any motor function milestones according to trial data. For Zolgensma, the short-term model data was shared by the manufacturer. All patients achieved motor function milestones. Based on the observed data, we assumed that a third of patients in the “sitting” health state in this arm also received Spinraza at the end of the short-term model, with an additional assumption that 50% of those who received the additional Spinraza treatment dropped a milestone (to “not sitting”).

Mortality for patients on Spinraza and BSC were derived from the ENDEAR and SHINE, and ENDEAR trials, respectively.^{22,26} No patient on Zolgensma died,²² and while we modeled this as per trial data, we acknowledge the uncertainty around this due to the small sample size in the Zolgensma trial. Inputs on permanent ventilation were derived from the ENDEAR and SHINE, and SHINE trial for Spinraza and BSC, respectively.^{22,26} As per Zolgensma’s trial data, we modeled no transition to permanent ventilation for patients in this treatment arm.²²

In the later onset SMA (Type II/III) population, based on trial data, all patients on Spinraza and BSC remained in the sitting health state in the short-term model. No data exists for Zolgensma in this population. For the pre-symptomatic SMA population, data on Spinraza’s effectiveness in achieving motor function milestones was derived from the NURTURE trial,²¹ and assumed that 60%, 30% and 10% of all patients in this group had SMA Types I, II and II, respectively, based on real-world evidence on *SMN2* copies predicting SMA type.^{2,3}

For the long-term model, patient proportions in different health states (“permanent ventilation,” “not sitting,” “sitting,” or “walking”) based on motor function milestones at the end of the short-term model were assumed to remain unchanged until death. In a more conservative scenario

analysis, we assumed deterioration of milestones, specifically from the “sitting” health state. We modeled transition to “permanent ventilation” or “death” from the “not sitting” health state in the BSC arm alone. For those “not sitting” who transition to death, we included the cost of permanent ventilation in the three months leading to death. Patients in the “not sitting” and “permanent ventilation” health state were assumed to have the same mortality, to account for the survival benefit gained from achieving interim milestones for those on the interventions when in the “not sitting” health state. This is an assumption favorable to the drug given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit. Mortality from all health states were modeled using best fitting parametric curves that were derived from digitized published Kaplan Meier (KM) curves.^{17,40,41} Details on this can be found in Section 4 and Appendix Tables E3-E6 of the report.

Utility estimates for patients in the different health states were derived from several sources.^{42,43,44} Patients in the walking state were attributed general population age-dependent utilities. We assumed additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as an additional utility of 0.1 compared to BSC for the “not sitting” health state and an additional utility of 0.05 compared to BSC for the “sitting” health state. Costs in the models included those of the interventions, their associated administration and monitoring costs, and costs of health care resources used, as well as non-medical costs associated with professional caregiving. A detailed sub-section of costs used in the model can be found in Section 4 of the report. For Spinraza, due to the nature of its administration in a hospital setting, we included a hospital mark-up. For Zolgensma, we used a placeholder one-time cost of \$2 million for the base-case analysis. For a scenario analysis using a modified societal perspective, we also included societal costs in the form of patient productivity gains costs.

In addition to the base-case analyses, we conducted one-way and probabilistic analyses, threshold analyses (for price) as well as specific scenario analyses. Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. Some of the key scenarios include 1) a modified societal perspective, 2) excluding health care costs directly related to treatment, 3) a comparison of Zolgensma to Spinraza, 4) using different utility or cost estimates, 5) not accounting for the utility benefit gained from achieving interim milestones, 6) shorter time horizon, and 7) alternative discount rate. A full list of scenario analyses conducted is available in Section 4 of the report.

Model Validation

Several approaches were undertaken to validate the model. First, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. Second, model input parameters were varied to evaluate the face validity of changes in results. As part of ICER’s initiative for modeling transparency, we

shared the model with AveXis for external verification shortly after publishing the draft report for this review. Biogen chose not to receive the model. The outputs from the model were validated against the trial and study data of the interventions as well as any relevant observational datasets. Finally, the results were compared to other cost-effectiveness models in this therapy area.

Results

Infantile-Onset (Type I) SMA Model

Results from the health care sector perspective for both interventions are presented below in Tables ES11 and ES12. Results for Zolgensma were derived using a placeholder price of \$2,000,000. Both interventions resulted in more QALYs and life years gained relative to BSC, resulting in incremental cost effectiveness ratios of approximately \$1.1 million per QALY for Spinraza and approximately \$243,000 per QALY for Zolgensma. The cost per life year (LY) gained for Spinraza and Zolgensma were approximately \$590,000 and \$182,000, respectively.

Table ES11. Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	3.24	7.64	\$1,112,000	\$590,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table ES12. Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,657,000	\$3,657,000	12.23	18.17	\$243,000	\$182,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We found from the one-way sensitivity analyses that the utility when in the “sitting” health state and the health care costs in the “not sitting” health state influenced model results the most for Spinraza, and for Zolgensma the factors that most affected the results were the cost and utility associated with the “sitting” health state. Probabilistic analyses showed that for Spinraza, none of the simulations produced incremental results that were cost-effective up to a threshold of \$500,000

per QALY. For Zolgensma, all simulations produced results that were cost-effective at and above a threshold of \$300,000 per QALY.

The modified societal perspective scenario analyses produced results very similar to those seen using the health care sector perspective. The results of the modified societal perspective analysis are presented in the main report in Tables 4.17 and 4.18. In the scenario analysis excluding intervention background health care costs, results were more favorable to both interventions with incremental cost effectiveness ratios versus BSC at approximately \$810,000 per QALY for Spinraza and approximately \$170,000 per QALY for Zolgensma.

Table ES13 presents the results for a scenario analysis comparing Zolgensma with Spinraza from the health care sector perspective. Instead of a naïve comparison that used the costs, QALYs, and LYs for Zolgensma and Spinraza from their respective comparisons with BSC, we performed a separate analysis incorporating the add-on costs of Spinraza in the Zolgensma arm (as opposed to assuming that a proportion of the patients lose a milestone in the base-case analysis). This analysis assumed that 33% of the patients in the “sitting” state of the Zolgensma arm (i.e., 25% of overall patients) receive Spinraza according to the standard dosing regimen after the end of the short-term model.

The total costs in the Zolgensma arm were approximately \$5.3 million with 13.46 QALYs and 19.76 LYs gained. The costs are higher than in the base case for Zolgensma versus BSC due to the additional costs associated with Spinraza treatment. However, the QALYs and LYs are also higher than in the base case, as this analysis does not assume any loss of milestones. The total costs in the Spinraza arm were around \$3.9 million with 3.24 QALYs and 7.64 LYs gained. This resulted in an incremental cost per QALY gained of approximately \$139,000 and an incremental cost per LY gained of \$117,000 for Zolgensma compared to Spinraza.

Table ES13. Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$3,630,000*	\$1,671,000	\$5,301,000	13.46	19.76	\$139,000	\$117,000
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of \$2 million) and additional Spinraza costs.

Results of all other included scenario analyses produced results similar to the base-case analyses for both interventions. These results can be found in Tables 4.20 and 4.21 of the report for Spinraza and Zolgensma, respectively.

Later Onset (Type II/III) SMA Model

Results for this population are specific to Spinraza alone since no published data on Zolgensma's effectiveness in this population exists. Since none of the patients were able to walk as per trial data in this population, QALY differences were minimal between Spinraza and BSC, with Spinraza resulting in marginally more QALYs due to utility benefit associated with achieving interim milestones.

Table ES14. Results for Spinraza versus BSC in Later Onset SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$7,634,000	\$1,514,000	\$9,148,000	12.28	18.90	\$8,156,000	Dominated
BSC	\$0	\$1,442,000	\$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

One-way sensitivity analyses were not performed for this model as parameters were the same in both arms, except for drug cost and the utility benefit for achieving interim milestones in the Spinraza arm, which was considered in scenario analyses. Probabilistic analyses showed that Spinraza did not achieve a greater than zero likelihood of meeting the \$500,000/QALY or lower threshold across the range of values tested. Results from the societal perspective scenario analysis were similar to those from the health sector perspective. Other scenario analyses results pertaining to this population are presented in Table 4.3 and Appendix Tables E32 to E34 of the report. Threshold analyses indicated that no annual price of Spinraza was attainable at the \$50,000 per QALY threshold due to the additional fixed administration costs coupled with a marginal utility benefit in the Spinraza arm for achieving interim milestones. At other thresholds between \$100,000 per QALY and \$500,000 per QALY its annual price ranged from approximately \$1,100 to approximately \$20,000 in this target population.

Presymptomatic SMA Model

Results for the presymptomatic SMA population are specific to Spinraza alone since no published data on Zolgensma's effectiveness in this population exists. It must be noted that these results are based on the proportion of Type I, II, and III SMA patients derived primarily from natural history data and these results may not be generalizable to a population with different proportions. From the health care sector perspective, the cost per QALY and cost per LY gained were approximately \$709,000 and \$652,000 respectively (Table ES15).

Table ES15. Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$10,565,000	\$1,364,000	\$11,929,000	21.94	26.58	\$709,000	\$652,000
BSC	\$0	\$801,000	\$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

The key drivers of uncertainty included monthly costs in the “walking” health state and the utility in the “sitting” health state. Spinraza did not achieve a greater than zero likelihood of meeting \$500,000/QALY or lower thresholds across the range of values tested.

In a scenario analysis taking a modified societal perspective, the cost per QALY and cost per LY gained were approximately \$687,000 and \$632,000, respectively. A list of additional scenario analyses results specific to this population are listed in Table 4.34 and Appendix Tables E39 to E43 of the report.

We received comments suggesting that Zolgensma could be approved by the FDA with an indication encompassing use among presymptomatic patients. Since there are no data on the effectiveness of Zolgensma in this population, we decided to conduct a scenario analyses for a hypothetical drug (“Drug X”) treatment which had the one-time costs of Zolgensma with the unrelated health care costs, QALYs, and LYs associated with Spinraza in presymptomatic SMA patients. This analysis which was conducted from a health care sector perspective resulted in Drug X having a cost per QALY and cost per LY gained at approximately \$157,000 and \$144,000, respectively (Table ES16).

Table ES16. Hypothetical Drug X for Presymptomatic SMA: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	\$3,264,000	21.94	26.58	\$157,000	\$144,000
BSC	\$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Threshold analyses indicated that Spinraza’s annual price to achieve thresholds of \$50,000 to \$500,000 per QALY ranged from approximately \$8,000 to approximately \$264,000 in this target population.

Limitations

Our analyses have several limitations that are fully addressed in the main report. Despite remaining uncertainty, we believe that the additional scenario analyses and sensitivity analyses allowed us to have confidence that our base-case results represent the best estimate of the clinical and economic effects of treatment.

Summary and Comment

For Spinraza, our base-case results found that, at its current price, it does not meet traditional cost-effectiveness thresholds in any population of use. Its cost-effectiveness is best in the presymptomatic population, but even there its price would need to be reduced below \$65,000 per year to meet a \$150,000 per QALY threshold. For later-onset SMA the incremental cost-effectiveness of Spinraza was over \$8 million per QALY gained, as current evidence did not demonstrate life extension and the benefits of treatment translate to small improvements in quality of life compared to best supportive care.

For Zolgensma at a placeholder price of \$2 million, our base-case results found that it too does not meet traditional cost-effectiveness benchmarks for use for patients with Type I SMA and would have to have its price reduced to under \$900,000 for the one-time administration to meet a \$150,000 per QALY threshold. However, using a cost per LYG threshold, the price for Zolgensma could be set near \$1.5 million to meet a \$150,000 per LYG threshold.

In order to provide policymakers with a broad view of cost-effectiveness, we have sought to enhance the visibility of the cost per LY gained results in conjunction with those arising from cost per QALY calculations. The cost per LYG approach values any life extension, even at a very low quality of life, as equal to life extension at full health. Cost per LYG does not capture improvements in quality of life as intended by ICER's stated goal of highlighting an "equal value for life-year gained" (evLYG) measure, but for this review it was not possible to construct a feasible technical approach to create an evLYG for this model. Therefore, viewing results of both the cost per LY gained and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group.

Our economic evaluation included multiple analyses targeting different SMA sub-populations. We also conducted numerous scenario analyses to explore questions about the best way to model the connection between motor skill improvements and quality of life, the impact of different time horizons and of a societal perspective on modeling results, and the relevance of substantial non-drug health care costs that continue to accrue when a treatment extends life. Except for one scenario analysis, we assumed in all other analyses that the short-term benefits of both treatments persist for a lifetime. Although there remains substantial uncertainty about whether this will prove true, input from clinical experts and judgments based on the mechanism of action of the two

treatments leads us to believe that our base-case assumption of lifetime durability of benefit, while it may be viewed as optimistic by some, is the best starting point for a judgment of the value of these treatments at this time.

Among the most challenging aspects of this cost-effectiveness analysis has been uncertainty about the future clinical use of these treatments. Will they be used primarily for presymptomatic patients? With data demonstrating effectiveness of Spinraza in this population, this evolution seems quite likely, a judgment confirmed by input from clinical experts. For Zolgensma the future is less clear due to the fact that it has not yet been studied in presymptomatic patients. But with the possibility of its use in this population we decided to create a hybrid “Drug X” that had the placeholder cost of Zolgensma and the effectiveness of Spinraza in this population. Given that Drug X is administered as a one-time infusion, we found its cost-effectiveness very near traditional ranges assuming a placeholder price of \$2 million. There is obviously substantial uncertainty in the potential effectiveness of Zolgensma in the presymptomatic population, but our hypothetical Drug X results may serve as a starting point for policy debates should the FDA approval language suggest that Zolgensma may be used in this population even without supporting clinical data.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES17. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Zolgensma is a one-time, intravenous administration which may reduce complexity and reduce caregiver burden compared with repeated lumbar punctures with Spinraza. As a one-time administration, there may also be reduced complexity for patients and caregivers navigating insurance policies.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	No impact identified.
This intervention will significantly reduce caregiver or broader family burden.	Effective treatment with Spinraza or Zolgensma may reduce anxiety and stress among caregivers and wider communities. As a one-time, intravenous injections, Zolgensma may also reduce reduced burden for patients and caregivers. Furthermore, effective treatment with Spinraza or Zolgensma may lead to incremental improvements in motor abilities, which can allow patients greater ability for self-care and independence.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Spinraza has a novel mechanism of action and is the first FDA approved treatment that modifies disease progression. Zolgensma is a novel gene therapy which also modifies disease progression.
This intervention will have a significant impact on improving return to work and/or overall productivity.	For both interventions, if treatment improves or retains children's mobility, children may attend school and caregivers may return to work.
This intervention will have a significant positive impact outside the family, including communities.	Effective treatment with Spinraza or Zolgensma may reduce other resources used (e.g., in schools) and promote more interaction between children with SMA and others in the community.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	Spinraza is the first FDA approved treatment that modifies disease progression. The availability of a disease-modifying treatment has paved the way for newborn screening, which may help to identify and subsequently treat infants with SMA sooner.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	No impact identified.

Contextual Considerations

Table ES18. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	SMA is a condition of particularly high severity and rapid progression, with the most severe cases affecting infants and young children. In the most common and severe form of SMA, estimates of the median age at death range from 10.4 months up to four years.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	SMA is a genetic condition that affects patients and caregivers throughout their lives. Supportive care does not modify disease progression, and patients may be entirely dependent on family members who expend intense emotional and physical effort when constantly caring for a patient.
This intervention is the first to offer any improvement for patients with this condition.	Spinraza is the first FDA approved treatment that modifies disease progression.
There is significant uncertainty about the long-term risk of serious side effects of these interventions.	Uncertainties remain regarding the long-term use of Spinraza with respect to repeated lumbar punctures. The long-term safety of a gene therapy like Zolgensma has not been established.
There is significant uncertainty about the magnitude or durability of the long-term benefits of these interventions.	The long-term effects of Spinraza or Zolgensma will take time to emerge as SMA is a rare disease and the trials have short-term follow-up.
There are additional contextual considerations that should have an important role in judgments of the value of these interventions.	No impact identified.

Value-Based Benchmark Prices

Our value-based price benchmarks for Spinraza and Zolgensma are presented in Table ES19. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY gained. Value based prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma. We did not use the modified societal analysis results as a dual base case for this review because we did not feel these drugs met the criterion that “the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs” as described in the [Value Assessment Framework for Ultra Rare Diseases](#).

We note that for treatments of ultra-rare disorders, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to

coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than those applied to decisions about other treatments. We there include below full threshold price analyses for both drugs, ranging from \$50,000-\$500,000 per QALY and per LYG.

For Spinraza, we believed that the most relevant population on which to base a value-based price benchmark is the presymptomatic SMA population. This decision is based upon our judgment that Spinraza is most likely to be used in this population now that there are data supporting its effectiveness. SMA has been added to the Recommended Uniform Screening Panel for newborns in the US,⁴⁵ making it likely that many patients will be identified and treated before symptoms develop. Given the greater magnitude of clinical benefit seen in this group, our results suggest that the cost-effectiveness of Spinraza is best when used before symptoms appear.

For Zolgensma, the value-based benchmark price was estimated in the SMA Type I population as this is the only population in which it has been evaluated, and although its use in presymptomatic infants will be considered by clinicians and families, data are not yet available from its use in this population.

Table ES19. Value-Based Benchmark Prices of Spinraza and Zolgensma

	List Price + Estimated Mark-Up	Population	VBP at \$100,000 per QALY Threshold	VBP at \$150,000 per QALY Threshold	Discount Required to Achieve Threshold Prices
Spinraza	\$382,500	Presymptomatic SMA	\$36,400*	\$64,800*	83% to 90%
Zolgensma	\$2,000,000†	Infantile-Onset (Type I) SMA	\$310,000	\$899,000	N/A as real-world price is unknown

QALY: quality-adjusted life year, VBP: value-based benchmark price

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+. Year one value-based benchmark prices are \$72,800 to \$129,400 due to the required loading doses.

†Placeholder price.

As described earlier, we are increasing reference to the cost per LYG figures to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which Spinraza meets the \$100,000 to \$150,000 per LYG range for use in presymptomatic patients is \$41,400 to \$72,300. This range is quite similar to the cost/QALY range. For Zolgensma, however, there is notable difference. The relevant cost per LYG price range for Zolgensma when used for Type I SMA is \$710,000 to \$1,498,000 for the \$100,000 to \$150,000 per LYG thresholds.

Broader Threshold Price Analyses

Table ES20 presents the threshold price results for Spinraza compared to BSC for presymptomatic individuals at thresholds from \$50,000 to \$500,000 per QALY gained and per LY gained. Threshold prices are reported as annual costs for Spinraza, including administration fees.

Table ES20. Threshold Prices for Spinraza in Presymptomatic SMA

	Per QALY*	Per LY Gained*
Threshold Price at \$50,000/QALY	\$8,000	\$10,500
Threshold Price at \$100,000/QALY	\$36,400	\$41,400
Threshold Price at \$150,000/QALY	\$64,800	\$72,300
Threshold Price at \$200,000/QALY	\$93,200	\$103,000
Threshold Price at \$300,000/QALY	\$150,000	\$165,000
Threshold Price at \$500,000/QALY	\$264,000	\$289,000

LY: life-year, QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table ES21 presents the threshold price results for Zolgensma compared to BSC in Type I SMA at thresholds from \$50,000 to \$500,000 per QALY gained and per LY gained. Threshold prices are reported for the one-time cost for Zolgensma.

Table ES21. Threshold Prices for Zolgensma in Type I SMA

	Per QALY*	Per LY Gained*
Threshold Price at \$50,000	--	--
Threshold Price at \$100,000	\$310,000	\$710,000
Threshold Price at \$150,000	\$899,000	\$1,498,000
Threshold Price at \$200,000	\$1,488,000	\$2,287,000
Threshold Price at \$300,000	\$2,666,000	\$3,865,000
Threshold Price at \$500,000	\$5,021,000	\$7,020,000

LY: life-year, QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential budgetary impact of Zolgensma in the SMA Type I population relative to BSC. Given that Spinraza is currently available, we conducted a scenario analysis in which we measured the potential budgetary impact of Zolgensma relative to a 75:25 Spinraza:BSC mix in the same patient population. Our analyses were conducted using the placeholder price (\$2 million), price to reach \$150,000 per QALY (\$898,976) and \$100,000 per QALY (\$310,097) thresholds for Zolgensma, and the scenario analysis used the net price for Spinraza. Because of high background health care costs in SMA, there was no price of Zolgensma that

achieved an incremental cost effectiveness ratio of \$50,000 per QALY. Based on published estimates, we calculated the incident SMA Type I population at 215 patients each year.

Table ES22 and ES23 illustrate the results of our budget impact analyses. Compared to BSC alone, the annual per-patient potential budgetary impact for Zolgensma ranged from approximately \$174,500 at the price to reach the \$100,000 per QALY threshold to approximately \$946,300 at its placeholder price. At Zolgensma's placeholder price, treating the entire target population would reach approximately 45% of the ICER annual potential budget impact threshold of \$991 million. Compared to the Spinraza:BSC mix, Zolgensma's annual per-patient potential budgetary impact ranged from cost-savings of approximately \$198,700 at the price to reach the \$100,000 per QALY threshold to approximately \$573,100 in additional costs at its placeholder price. In this scenario, treating the entire target population would reach 24% of the \$991 million threshold using the placeholder price for Zolgensma.

Table ES22. Per-Patient Budget Impact Calculations for Zolgensma Compared to BSC, Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	\$150,000/QALY	\$100,000/QALY
Zolgensma*	\$1,113,600	\$610,800	\$341,900
BSC	\$167,400		
Difference	\$946,300	\$443,500	\$174,500

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

All costs rounded to the nearest \$100.

*Based on a placeholder price of \$2,000,000.

Table ES23. Per-Patient Budget Impact Calculations for Zolgensma Compared to Spinraza/BSC (75%/25%), Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	\$150,000/QALY	\$100,000/QALY
Zolgensma*	\$1,113,600	\$610,800	\$341,900
Spinraza/BSC (75%/25%)	\$540,600		
Difference	\$573,100	\$70,300	-\$198,700†

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

All costs rounded to the nearest \$100.

*Based on a placeholder price of \$2,000,000.

†Cost-saving.

With the recent FDA recommendation on newborn screening for SMA and its increasing adoption in many states,^{45,46} we felt it pertinent to include a scenario comparing Spinraza to BSC in the presymptomatic SMA population. Due to a lack of published data on the efficacy of Zolgensma in

this particular population, we could not undertake a similar budget impact analysis for the gene therapy. At Spinraza's net price, the per patient annual potential budgetary impact versus BSC was estimated to be approximately \$573,900. When treating the entire eligible population (approximately 370 patients annually), potential budget impact reached 58% of the \$991 million threshold.

1. Introduction

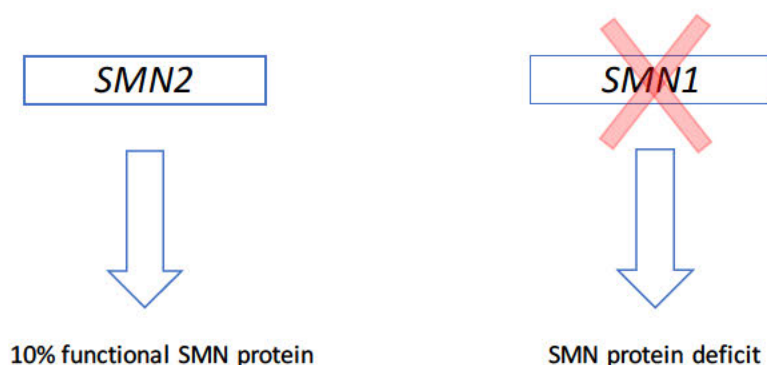
1.1 Background

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease caused by mutations in the survival motor neuron (*SMN*) gene that encodes the SMN protein. The SMN protein is essential for the development and maintenance of motor neurons, which control muscle movement. A deficiency in SMN protein causes irreversible degeneration of motor neurons, which clinically manifests as progressive muscle weakness such that patients may have difficulty moving, swallowing, or breathing.¹

The most common form of SMA has been mapped to chromosome 5q, which contains two *SMN* genes.⁵ The telomeric copy of the gene (*SMN1*) and the centromeric copy of the gene (*SMN2*) are nearly identical and both encode the SMN protein. A difference in the genes at a single nucleotide produces an alternative splicing of exon 7, which affects the structure of the resulting SMN protein.⁴⁷ Using the information from *SMN1*, a full-length and fully functional SMN protein is created. In contrast, 80-90% of the SMN protein generated from each *SMN2* is nonfunctional (Figure 1.1), although individuals typically have two to four copies of *SMN2*. Hence, most of the functional SMN protein is created by *SMN1*, and mutations in *SMN1* are associated with development of SMA.⁴⁷ Although the number of *SMN2* copies modulates the severity of SMA, patients without a functional copy of *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.^{7,47}

Figure 1.1. Genetics of SMA



SMA is commonly caused by homozygous deletion or deletion and point mutation of the alleles in the survival motor neuron 1 (*SMN1*) gene that mainly produces full-length SMN protein (right). The *SMN2* gene differs from *SMN1* by a few nucleotides, such that only 10% of the SMN protein it generates is fully-functional (left).

In the United States (US), SMA incidence is approximately one in 10,000 live births or about 500 new SMA cases per year.³ The most severe cases of SMA affect infants and young children, and the disease rapidly progresses once symptoms present.^{1,2} Muscle weakness commonly presents as weakness of the limbs, especially in the muscles of the torso, upper legs, and upper arms, and patients may have difficulty swallowing or breathing. Historically, life expectancy in the most common and severe form of SMA (Type I) was less than two years. In part due to improvements in standard of care, more recent estimates of the median age at death in this type of SMA range from ten months up to four years.^{30,48,49} Survival depends on respiratory function, and many infants and children eventually require permanent ventilation. SMA does not affect cognitive function, and there is often a contrast between a patient's alertness and ability to move.

SMA subtypes are classified into clinical groups based on age of onset and maximum motor function achieved (Table 1.1).^{2,8} Clinical severity also depends on the level of SMN protein, which is related to the number of *SMN2* copies as noted above.

Table 1.1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of <i>SMN2</i> Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.²

Number of *SMN2* copies based on Calucho et al. 2018.⁹

Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth. Type I SMA (infantile-onset SMA) represents approximately 60% of all diagnosed SMA cases.³ These patients typically have one to three copies of *SMN2*,⁹ present with symptoms before six months of age, do not achieve key motor milestones (e.g., sitting without support), and lose motor functioning over time. Muscles in the respiratory and digestive tracts are also affected, which can cause breathing complications, difficulty swallowing, and constipation. Patients may die or need permanent respiratory support within two years of life.³ Approximately 20-30% of patients diagnosed with SMA have Type II.^{2,3} Type II SMA presents between six to 18 months of age with patients typically having three copies of *SMN2*, although some have two or four copies.⁹ These patients cannot walk independently, and most patients survive to adulthood with aggressive supportive care.³ Approximately 10-20% of patients diagnosed with SMA have Type III.^{2,3} Type III SMA presents in patients aged 18 months to 18 years, and patients typically have three or four copies of *SMN2*.⁹ Patients have a normal life expectancy and can walk independently, although they may lose this ability over time. Type IV SMA, a very rare

and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.^{2,8}

Diagnosis and Care

Diagnosis of SMA is typically prompted by the clinical symptoms of muscle weakness described above. In part because of SMA's rapid progression and the importance of early treatment to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the US.⁴⁵ Diagnosis is based on a genetic molecular test. SMA is autosomal recessive, meaning that two copies of *SMN1* must have mutations in order for SMA to develop in an individual. In most patients with SMA, the disease is caused by homozygous deletion or deletion and point mutation of the alleles of *SMN1*.⁴⁻⁶ Although the number of *SMN2* copies does not confirm the diagnosis of SMA, it is strongly correlated with the severity of disease and may be an important aspect when considering treatment options.

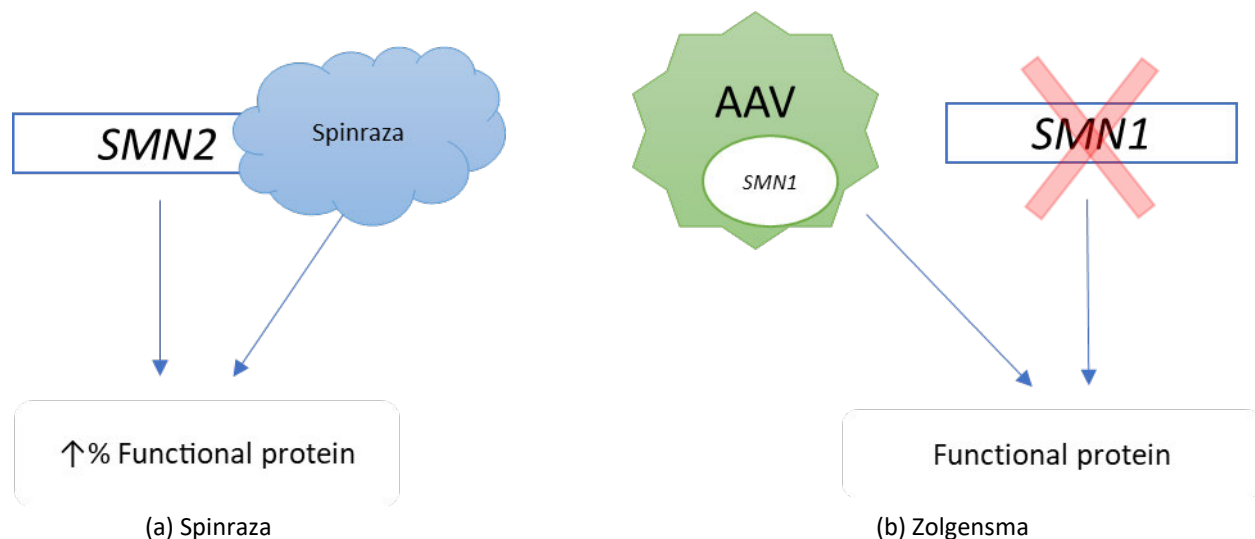
Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.¹⁰⁻¹² Nevertheless, supportive care does not modify disease progression, and patients may be entirely dependent on family members and caregivers. The intense emotional and physical effort involved with caring for a patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.^{13,14} Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Disease-Modifying Therapies

Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.¹⁵ Spinraza, an antisense oligonucleotide, targets the messenger RNA from *SMN2* so that it creates more functional SMN protein (Figure 1.2a). It is administered via intrathecal injection (i.e., into the cerebrospinal fluid that surrounds the spinal cord and brain) with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter. Spinraza has been studied in patients with or likely to develop SMA Types I-III,¹⁶⁻¹⁸ with several studies ongoing.¹⁹⁻²¹ In December 2016, the US Food and Drug Administration (FDA) approved Spinraza for the treatment of SMA (any subtype).¹⁵

A new gene therapy, Zolgensma® (onasemnogene abeparvovec, Novartis/AveXis), is currently in development to treat patients with SMA. Zolgensma, formerly known as AVXS-101, uses the adeno-associated virus serotype 9 vector (AAV9) to deliver a copy of the *SMN* gene to replace the defective *SMN1* gene (Figure 1.2b).²² Zolgensma is being studied as a one-time, intravenous administration in patients with Type I SMA. The FDA granted Zolgensma a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected by mid-2019.²³

Figure 1.2. Disease-Modifying Interventions for SMA



The availability of a disease-modifying therapy has altered the landscape of SMA management. Nevertheless, important uncertainties remain regarding the effectiveness of Spinraza in certain patient subgroups (e.g., type of SMA and duration of symptoms) and its duration of benefit. There are additional uncertainties around Zolgensma and its comparative effectiveness with Spinraza. With both agents, it is uncertain how well the cost of therapy is aligned with benefits. All stakeholders will benefit from a comprehensive review of the clinical evidence on both drugs and an analysis of their long-term cost-effectiveness and potential budget impact.

1.2 Scope of the Assessment

Overview

This report assesses the comparative clinical effectiveness and economic impacts of Spinraza and Zolgensma versus supportive care for patients with SMA. The assessment aims to systematically evaluate the existing evidence, taking uncertainty and patient-centered considerations into account. To that aim, the assessment is informed by two research components (a systematic review of the existing evidence and an economic evaluation) developed with input from a diverse group of stakeholders, including patients and their families, clinicians, researchers, representatives from SMA patient advocacy groups, and manufacturers of the agents of focus in this review. Below, we present the review's scope in terms of the research questions, PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements, and an analytic framework diagram.

Research Questions

The following research questions were developed with input from clinical experts, patients, and patient groups:

- 1) By type of SMA (Types 0-IV), what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes of:
 - Spinraza versus supportive care?
 - Zolgensma versus supportive care?
 - Spinraza versus Zolgensma?
- 2) In presymptomatic patients with SMA, what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes of:
 - Spinraza versus supportive care?
 - Zolgensma versus supportive care?
 - Spinraza versus Zolgensma?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS elements.

Populations

The population of focus for the review is infants, children, and adults with SMA. Where data are available, we will look at subpopulations defined by age of onset (including presymptomatic, infant-onset, later-onset), SMA subtype (0-IV), or number of *SMN2* copies.

Interventions

Our review will seek information on Spinraza and Zolgensma.

Comparators

Where data permit, we intend to compare the agents to each other and to supportive care (with or without sham administration).

Outcomes

The outcomes of interest are listed below.

Efficacy

- Mortality
- Permanent invasive ventilatory support
- Motor function, including:
 - Hammersmith Functional Motor Scale-Expanded (HFMSE)
 - Hammersmith Infant Neurological Examination-Section 2 (HINE-2)
 - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
 - Revised Upper Limb Module (RULM)
 - World Health Organization motor development milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, walking alone)
- Mobility (e.g., 6-Minute Walk Test)
- Bulbar function (e.g., swallowing, speaking)
- Use of respiratory or gastrointestinal support (e.g., gastrointestinal tube)
- Other complications of SMA (e.g., scoliosis)
- Quality of Life (e.g., PedsQoL)

Safety

- Treatment-related adverse events (AEs)
 - Injection or infusion site reactions
 - Thrombocytopenia and low platelets
 - Renal toxicity
 - Liver function (e.g., elevated aminotransferase)
 - Complications of lumbar puncture (e.g., back pain, vomiting, headache)
- Serious adverse events (SAEs)
- Adverse events leading to discontinuation

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

Settings

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

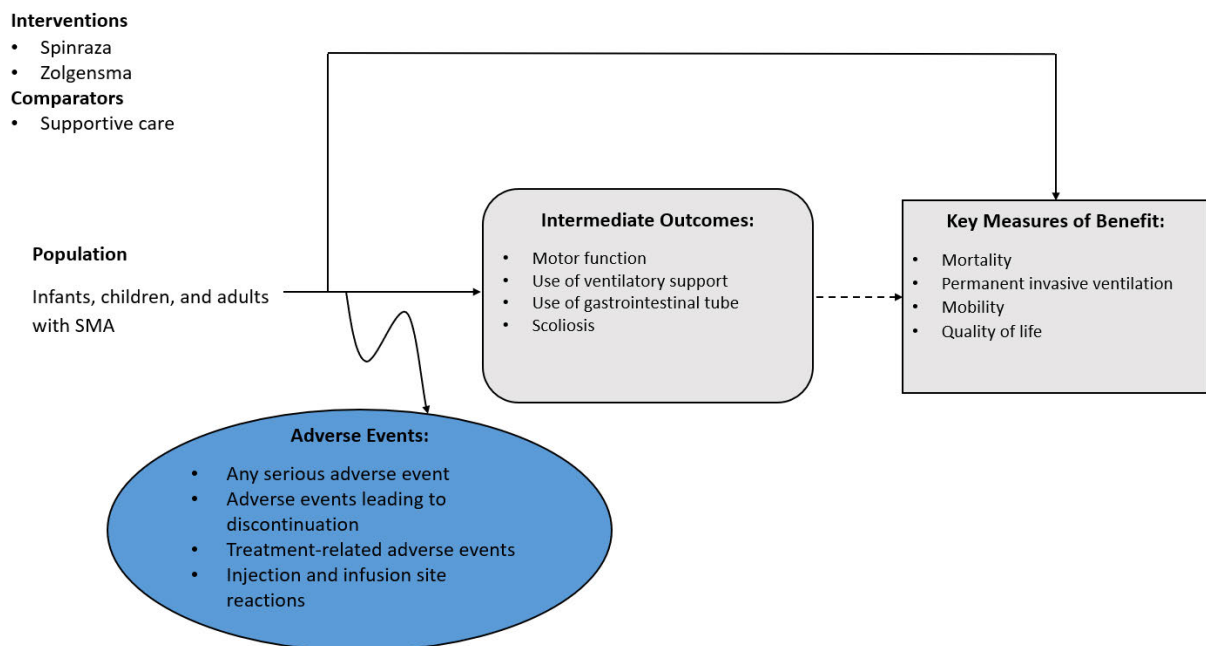
Study Design

Randomized controlled trials, non-randomized comparative studies, and single arm-studies with any sample size will be included.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.3.

Figure 1.3. Analytic Framework



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., use of ventilatory support), and those within the squared-off boxes are key measures of clinical benefit (e.g., quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.⁵⁰

Value Framework Considerations

ICER is assessing Spinraza and Zolgensma under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because the assessment meets the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

1.3 Definitions

Genes

SMN1: The telomeric copy of the *SMN* gene responsible for generating most of the functional SMN protein. Homozygous deletion or deletion and point mutation of the alleles of *SMN1* causes SMA.⁴⁻⁶

SMN2: The centromeric copy of the *SMN* gene, also referred to as the "SMN back-up gene," which generates only a limited amount of functional SMN protein. A higher number of *SMN2* copies can modulate the severity of SMA.

SMA Types

Type 0: Affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth.

Type I: Also called infant-onset SMA, patients present with symptoms before six months of age, do not reach key motor milestones (e.g., sitting without support), and lose motor functions over time. Patients may die or need permanent respiratory support within two years of life, although survival has increased in recent years due to advancements in supportive care.^{3,30,48,49}

Type II: This type of SMA together with Type III is also referred to as later-onset SMA. Patients with Type II SMA present between six to 18 months of age, cannot walk independently, and survive to adulthood with aggressive supportive care.³

Type III: This type of SMA together with Type II is also referred to as later-onset SMA. Patients with Type III present between 18 months to 18 years of age, and have a normal life expectancy, and can walk independently, although they may lose this ability over time.³

Type IV: A very rare and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.^{2,8}

Outcomes

Hammersmith Functional Motor Scale-Expanded (HFMSE): An expanded version of the Hammersmith Functional Motor Scale (HFMS) to evaluate ambulatory SMA patients (i.e., Type II or III SMA). The HFMS is a clinician-rated, 20-item scale developed to assess the motor ability of children with SMA with limited ambulation. The HFMSE extends the HFMS by adding 13 items from the Gross Motor Function Measure (GMFM), a measure developed for assessing change in motor function in children with cerebral palsy. Each item in the HFMSE is measured on a 3-point scale with higher scores indicating better functioning. Untreated patients with SMA Type II or Type III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.^{33,34}

Hammersmith Infant Neurological Examination-Section 2 (HINE-2): HINE assesses development of neurological function in healthy infants. Section 2 in HINE focuses on motor milestone achievement, which is an area typically not attained by infants with SMA. HINE-2 consists of eight items to assess infants' changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Partial attainment of a skill can be captured in subscores. Each milestone is measured on a 3- to 5-point scale with higher scores indicating better functioning. Untreated patients with SMA Type I are unlikely to attain a score of >1 in any milestone.^{51,52}

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND): A validated 16-item scale designed to capture motor function in SMA infants with Type I. Each item is measured on a 5-point scale (total 0–64 points) with higher scores indicating better functioning.^{53,54}

Revised Upper Limb Module (RULM): An assessment of 19 tasks designed to assess upper limb function in non-ambulatory patients with SMA. Each item is measured on a 3-point scale with higher scores indicating better functioning.³⁵

World Health Organization (WHO) Motor Development Milestones: Captures six dichotomous yes/no motor skills (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, walking alone).⁵⁵ Age windows of achievement for healthy infants are in Table 1.2. Note that the six windows overlap, and the sequence of achievement varies. Most infants follow the order below with hands-and-knees crawling shifting between earlier or later milestones.

Table 1.2. Age Windows of Achieving Motor Development Milestones

	Sitting without Support	Standing with Assistance	Hands-and-Knees Crawling	Walking with Assistance	Standing Alone	Walking Alone
Age in Months, 1st-99th Percentiles	3.8-9.2	4.8-11.4	5.2-13.5	5.9-13.7	6.9-16.9	8.2-17.6

Adopted from the WHO Multicenter Growth Reference Study Group.

6-Minute Walk Test (6MWT): A measure of ambulatory function, specifically how far an individual can walk within six minutes.⁵⁶

1.4 Insights Gained from Discussions with Patients and Patient Groups

Throughout the conceptualization of this review, we heard from patient advocates and caregivers how devastating the diagnosis of Type I SMA can be and how difficult it is to watch the disease progress in a child. Parents and caregivers feel helpless and fearful while also needing to be vigilant and constantly providing care. Care entails approaches to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. We heard from adults with SMA how frustrating it is that new interventions have not been commonly studied in adults and that more data are needed in this population, including data on appropriate dosages. Patients and caregivers reported wanting treatments that improve strength and the ability to live more independently. We also heard extensively about the importance of early identification of and treatment for SMA. In addition, six families submitted public comments on our [Draft Scope](#), which provided additional context on the experience of children with SMA and their parents. These comments described the devastating urgency of treatment and severity of SMA symptoms, and many described the positive impact of treatment.

To supplement our discussions and open input comments, we also reviewed the “Voice of the Patient” report, which summarizes a Patient-Focused Drug Development meeting hosted by Cure SMA in April 2017.²⁴ The meeting gathered patients' and families' perspectives on living with SMA and on current and future therapies. Many of the key themes from the meeting echoed those we heard from our conversations with caregivers and patient advocates. Additional themes related to burden of disease included communication challenges as children with SMA grow, the concern of developing scoliosis (particularly for patients with Type II), and the constant worry about further loss of functional ability. Additional themes related to treatment options included optimism about disease modifying treatments, an expectation that some symptoms will exist even with treatment, and a desire for treatments that improve strength and functional ability while also valuing treatments that stabilize the disease.

Following our scoping discussions and public comment periods, we updated our draft scope to include efficacy outcomes related to bulbar function (e.g., swallowing, speaking) to better reflect

what is important to patients with SMA and their families. Comments about families' experiences with SMA provided patient-centered context for interpreting clinical trial outcomes by communicating the importance of independent functioning for older children and adults with SMA, and delay of disease progression for infants and younger children with SMA. These comments particularly underscored the importance of not only improved mobility, but also slowed progression and stabilization of current motor functions including smiling and independent sitting, eating or feeding, toileting, and transferring from wheelchairs.

ICER also received public comments on its on its [Draft Evidence Report](#) from a mix of patients, patient advocacy organizations, manufacturers, and providers. All three families who provided public comments described children with SMA who are receiving Spinraza; these families all reported a positive outlook on treatment with Spinraza. We also heard from three patient advocacy organizations who provided context about the patient experience living with SMA as well as feedback on key decisions made in the cost-effectiveness evaluation. We also heard from patients at different time points in this review about the spillover effects of this disorder on patients' caregivers, mainly parents, and we explored approaches to incorporate this caregiver burden into our model accordingly. However, due to the methodological uncertainty in estimating caregiver quality of life over a long-term horizon, we did not include this in our analyses. Further details are provided in Section 4.

1.5 Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invited manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. For this report, no manufacturer submitted information on development or production costs that would be an important factor in justifying the price of their products.

1.6. Potential Cost-Saving Measures in SMA

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/final-vaf-2017-2019/>). These services are ones that would not be directly affected by Spinraza or Zolgensma (e.g., respiratory support), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SMA beyond the potential offsets that arise from a new intervention. Currently, we have not identified any potential cost-saving areas.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for Spinraza, we reviewed publicly-available coverage policies from the Centers for Medicare and Medicaid Services (CMS), MassHealth, Husky Health Connecticut, Vermont Medicaid, and from regional and national commercial insurers (Aetna, Blue Cross Blue Shield of Massachusetts [BCBSMA], Cigna, Harvard Pilgrim Health Care, Humana, and UnitedHealthcare [UHC]). At the time the evidence report was published, we were unable to survey policies pertaining to Zolgensma because the medication is not yet approved by the FDA. We were unable to locate any National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) for Spinraza.

To obtain coverage for Spinraza, all commercial payers require prior authorization. These requirements vary somewhat across payers but are largely consistent. All six commercial payers require a confirmed diagnosis of SMA Type I, II, or III. Aetna, BCBSMA, Harvard Pilgrim, and UHC specify that the diagnosis of SMA must be made by a neurologist. Aetna, Cigna, Humana, and UHC require the submission of medical records to document either 1) homozygous gene deletion or mutation, or 2) compound heterozygous mutation. Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the *SMN2* gene; Humana states that patients may have no more than two copies. To obtain coverage under Cigna and UHC, patients must not be dependent on invasive ventilation or tracheostomy, and must not require non-invasive ventilation except during sleep. In addition to results from genetic testing, several payers, including BCBSMA, Cigna, and UHC require results from one of the following exams to establish baseline motor ability: CHOP-INTEND, HINE-2, HFMSE, ULM, RULM, or 6MWT. Humana specifies that if approved, initial authorization is granted for three months, Cigna and Harvard Pilgrim grant authorization for six months, and BCBSMA grants authorization for up to one year.⁵⁷⁻⁶¹

Table 2.1. Private and Public Payer Coverage for Spinraza Based on Subtype and Genetic Criteria

Coverage Authorized Based on Subtype and Genetic Criteria									
	Subtype					Number of Copies of <i>SMN2</i>			
	Type 0	Type I	Type II	Type III	Type IV	1	2	3	4
Aetna	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
BCBSMA	NS	Yes	Yes	Yes	NS	NS	NS	NS	NS
Cigna	No	Yes	Yes	Yes	No	NS	NS	NS	NS
Harvard Pilgrim	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Humana	Yes	Yes	NS	NS	No	Yes	Yes	No	No
UHC	No	Yes	Yes	Yes	NS	No	Yes	Yes	Yes
MassHealth	No	Yes	Yes	Yes	No	NS	NS	NS	NS
Husky Health CT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
VT Medicaid	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes

BCBSMA: Blue Cross Blue Shield of Massachusetts, NS: not specified, *SMN2*: survival motor neuron 2, UHC: UnitedHealthcare

All payers list similar requirements for continued use of Spinraza. Each of the six commercial payers require a positive clinical response or improvement in motor milestones from the pretreatment baseline as demonstrated by results from one of the following tests: CHOP-INTEND, HINE-2, HFMSE, ULM, RULM, or 6MWT. If reapproved, Harvard Pilgrim grants authorization for an additional six months, Humana for an additional four months, and UHC for twelve months.⁵⁷⁻⁶¹

MassHealth, Husky Health Connecticut, and Vermont Medicaid require prior authorization in order to obtain Spinraza. Similar to the commercial payers surveyed, MassHealth requires a genetic test that confirms a diagnosis of SMA Type I, II, or III. Documentation from a neurologist must be provided, as well as results from a baseline motor function test.⁶²

The policy of Husky Health Connecticut is nearly identical to MassHealth, but the coverage guidelines are categorized by SMA type. For patients with Type I, both the diagnosis and the request for Spinraza must be made by a neurologist. Genetic testing must confirm the mutation/deletion in chromosome 5q (homozygous gene deletion, homozygous gene mutation, or compound heterozygous mutation) and that the patient has at least two copies of *SMN2*. The patient cannot be dependent on ventilation or tracheostomy or need non-invasive ventilation beyond use for sleep. Lastly, a baseline motor exam must be completed to determine motor ability. For any other SMA type, the policy lists the same requirements, but includes an additional note that the attending neurologist must include documentation as to why the patient should be treated with Spinraza. Continuation of therapy may be approved if the patient exhibits an improvement in motor ability as defined by a specified increase in a HINE, HFSME, ULM, or CHOP-INTEND score.⁶³

The policy of Vermont Medicaid is similarly comprehensive.⁶⁴ It specifies that the patient must have at least two copies of *SMN2* and must not be dependent on invasive or noninvasive ventilation for more than six hours per day. The policy requires the following four laboratory tests to be

conducted prior to each dose: platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine protein. For continuation of therapy, patients with Vermont Medicaid must submit documentation that supports an improvement or maintenance, or a slowed progression of disease.⁶⁴

2.2 Clinical Guidelines

We reviewed guidelines on SMA and Spinraza issued by major US clinical societies and working groups, as well as guidance from the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE). Guidelines pertaining to supportive care may be found in Appendix F.

American Academy of Neurology (AAN)

*Evidence in Focus: Spinraza Use in Spinal Muscular Atrophy (2018)*⁶⁵

The AAN states that Spinraza is beneficial to SMA patients with Types I or II in early or middle symptomatic stages, as these patients have the highest potential for improvement in motor function. There exists less evidence concerning the use of Spinraza in patients with milder forms of SMA, or those with advanced disease and disability. Moreover, as the AAN notes, the cost-benefit profile is less favorable in older patients with less severe disease or with very advanced disease, even though these populations may respond to treatment. The AAN states that future research on Spinraza should not only include studies with patients with more advanced disease and adults with Types III and IV, but should also include cost-benefit analyses for these different groups.

Additional comments and recommendations for treatment with Spinraza include the importance of early diagnosis (including screening tools to assess infants), psychological counseling, periodic evaluations by physicians and physical therapists, and the need for a joint approach to care among doctors, therapists, and families.

Canadian Agency for Drugs and Technologies in Health (CADTH)

*CADTH Canadian Drug Expert Committee Recommendation (Final) – Spinraza (Spinraza – Biogen Canada Inc.) (2017)*⁶⁶

The CADTH Canadian Drug Expert Committee (CDEC) recommends Spinraza in patients with infantile-onset (Type I) SMA. Negotiations surrounding price and coverage for patients with other types of SMA are still ongoing, and will be released in early 2019. The CDEC's guidance for Type I SMA was contingent on a substantial price reduction, and in October 2018, CADTH and Biogen completed their negotiations. In the resulting recommendations, CDEC notes that in clinical trials, patients with Type I SMA showed improved motor function compared with a sham procedure, and

had an overall lower risk of permanent ventilation. Based on these factors, the CDEC states that Spinraza should be administered to patients with Type I SMA who have a high probability of improvement in motor function and deferment of permanent ventilation.

National Institute for Health and Care Excellence (NICE)

***Appraisal Consultation Document: Spinraza for Treating Spinal Muscular Atrophy (2018)*⁶⁷**

In August 2018, NICE issued a provisional recommendation against treatment for SMA with Spinraza due to the lack of long-term evidence, and the subsequent uncertainty surrounding long-term benefits. In the document, NICE also cites uncertainties in the economic evidence, emphasizing the drug's considerably high list price. The appraisal committee does acknowledge that Spinraza shows substantial benefit compared to a sham procedure in clinical trials — especially for patients with early-onset SMA — but concludes that because the size and nature of long-term benefits is uncertain, it cannot recommend Spinraza as a cost-effective use of NHS resources. As of November 12, 2018, negotiations around pricing and coverage were still ongoing, and once complete, NICE will offer its final guidance on Spinraza.

3. Comparative Clinical Effectiveness

3.1 Overview

This review of clinical effectiveness of Spinraza and Zolgensma for SMA in comparison to supportive care was informed by the evidence from available clinical studies meeting the inclusion criteria (i.e., PICOTS), whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). The scope of this review is detailed in Section 1.2. In brief, this review focused on efficacy, safety, and effectiveness of Spinraza and Zolgensma in comparison to supportive care (with or without sham administration) in SMA patients of all ages and types. We sought evidence on the following key clinical outcomes: mortality, permanent ventilation, event-free survival, motor function and milestones, and safety (e.g., AEs, discontinuations due to AEs, SAEs). Other outcomes described in Section 1.2 were sparsely reported and are detailed in Appendix D, where available. None of the studies included in our review reported outcomes related to quality of life or scoliosis.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for SMA followed established best research methods.^{68,69} We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁷⁰ The PRISMA guidelines include a checklist of 27 items, which are listed in Appendix Table A1. This review was prospectively registered with PROSPERO (CRD42018112419) and the full research protocol is available online (<https://osf.io/ra46v/>).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, and Study Design elements described above. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and Emtree terms in EMBASE), as well as free-text terms. The full search strategy is available in Appendix Tables A2 and A3. The date of the most recent search is January 7, 2019.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references relevant to the scope of this project. We also supplemented our review of published studies with data from

conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see <http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

Study Selection

Studies meeting the PICOTS criteria described in Section 1.2 were eligible for our review. To be included, studies were required to assess Spinraza or Zolgensma (any dose or regimen) in infants, children, or adults with SMA with any number of *SMN2* copies. For any study that also assessed supportive care, we accepted and used the study's definition of supportive care. We excluded studies only assessing supportive care (e.g., comparative studies of different support care options or single-arm supportive care studies), studies comparing different lumbar puncture approaches using Spinraza, and studies where participants received a single dose of Spinraza because these studies do not reflect how Spinraza is used in practice. Case-control studies were also excluded.

Data Extraction and Quality Assessment

Data from included studies were extracted directly into Microsoft Excel. Data elements extracted include a description of patient populations (type of SMA, presymptomatic SMA, ventilation use at baseline, motor function at baseline, age at diagnosis and treatment initiation), sample size, duration of follow-up, funding source, study design features (randomization, location, frequency of visits), interventions (agent, dosage, frequency, schedules, and routes of administration), supportive therapy allowed and used (e.g., any pharmacologic or non-pharmacologic agent along with frequency and schedules), outcome assessments, results, and study quality assessment for each study.

We assessed the quality of randomized controlled trials and non-randomized comparative studies according to the criteria published by the US Preventive Services Task Force (USPSTF), using the categories “good,” “fair,” or “poor.”⁷¹ A study quality rating was not assigned to grey literature (conference abstracts/posters) because they lack granular details. The USPSTF criteria are summarized below.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important

outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Assessment of Level of Certainty in Evidence

We used the [ICER Evidence Rating Matrix](#) to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).⁷²

Assessment of Publication Bias

We assessed publication bias for Spinraza and Zolgensma using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. We consider the presence of any such studies indicative of publication bias. We did not find any such studies in our review of ongoing trials. See Appendix C for an overview of the ongoing trials we identified.

Data Synthesis and Statistical Analyses

For each outcome of interest, the results of the studies are presented in the text or tables. When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. We recognize the difficulty in validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. As such, we aim to add specific context to our findings regarding potential challenges in study design, when possible.

Analyses are descriptive only due to differences in entry criteria, patient populations, outcome assessments, lack of available patient-level data, and other factors that precluded formal quantitative direct or indirect assessments of Zolgensma and Spinraza versus each other or supportive care.

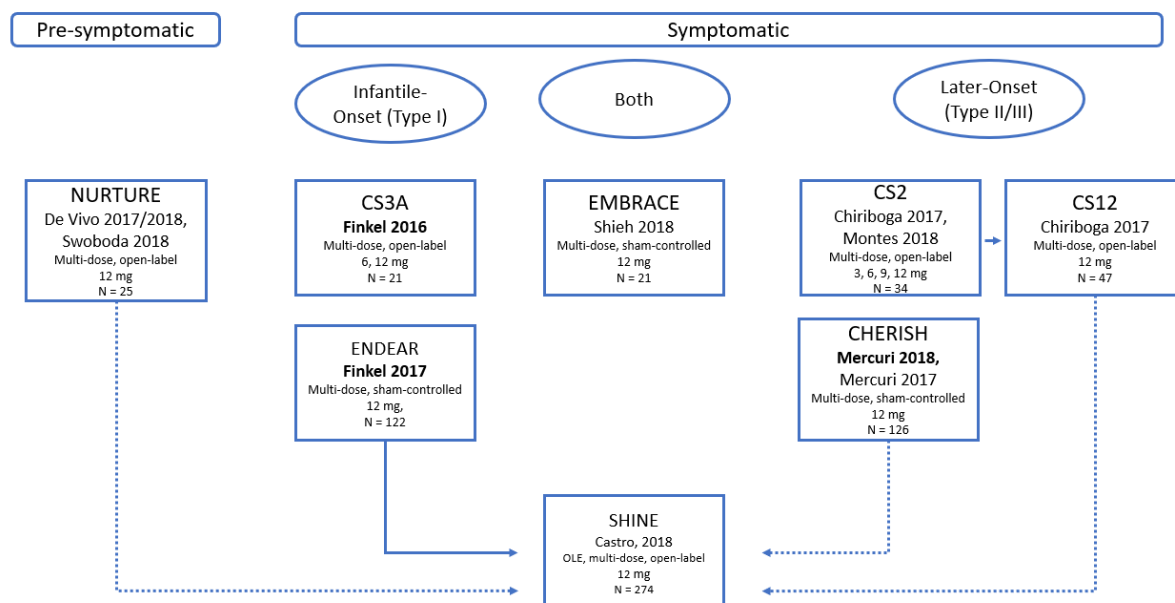
3.3 Results

Study Selection

Twenty-two references met the full PICOTS criteria (Appendix A, Figure A1). Primary reasons for exclusion were reporting of outcomes not relevant to this review and conference abstracts or posters reporting data subsequently published in peer-reviewed literature.

Overall, the 22 references correspond to six unique trials of Spinraza, one open-label extension (OLE) of Spinraza, five cohort studies of patients receiving Spinraza, and one trial of Zolgensma. Specifically, the Spinraza clinical trials include: one RCT with sham control (ENDEAR, one publication and two conference abstracts), and one open-label, dose-escalation study (CS3A; one publication and two conference abstracts) in Type I SMA; one RCT with sham control (CHERISH, one publication and one conference abstract) and one open-label, multiple dose study (CS2/12; one conference abstract and one conference poster) in Types II and III; one single-arm study (NURTURE, three conference abstracts) in presymptomatic SMA; and one RCT with sham control (EMBRACE, one publication and one conference abstract) in patients with Types I, II, or III SMA ineligible for the other trials (Figure 3.1). Patients who completed the above trials were eligible to enroll in an OLE (SHINE, one conference abstract), although results are currently available for only the patients with Type I SMA who had been enrolled in ENDEAR. In addition, we identified three cohort studies (three publications) of patients with Type I SMA receiving Spinraza through extended access programs (EAPs) and two cohort studies (two publications) in patients with Type II SMA.

Figure 3.1. Clinical Trials of Spinraza



Results are not yet available for the individuals who enrolled in SHINE from the trials indicated with dashed lines.

Finally, one publication and one conference presentation reported on the Zolgensma Phase I, two-cohort study, CL-101, and one publication on its long-term follow-up study, START, in patients with Type I SMA.

We found no trials or data on any treatment for newborns with SMA Type 0 or adults with Type IV.

Full details of all studies included in our systematic literature review are provided in Appendix D. Key trial details including participant characteristics and clinical benefits are presented below in the corresponding section by type of SMA (e.g., infantile-onset, later-onset, and presymptomatic). Harms are summarized together for all populations.

Quality of Individual Studies

We rated the quality of three sham-controlled RCTs: ENDEAR, CHERISH, and EMBRACE. As noted in the methods (Section 3.2), we did not rate the quality of non-comparative studies (e.g., NURTURE, CS3A, CS2/CS12, CL-101) or OLEs (SHINE, START).

We rated all three RCTs to be of good quality based on the USPSTF criteria. Additional details for each trial regarding the comparability of groups, participant blinding, validity of outcome assessments, intervention definitions, and key outcome reporting can be found in Appendix D. Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arms compared to the placebo arms. The direction of potential bias in the results is unclear. The differences in baseline characteristics are highlighted in the sections that follow.

Infantile-Onset (Type I) SMA

In infantile-onset (Type I) SMA, we included three clinical trials of Spinraza, including two sham-controlled RCTs (ENDEAR and EMBRACE)^{17,25} and one open-label, dose-escalation study (CS3A).¹⁶ We also included longer-term results for infants in ENDEAR who enrolled in the single-arm OLE (SHINE).²⁶ In addition, we included three cohort studies of patients receiving Spinraza through EAPs.⁷³⁻⁷⁵ Finally, we included a two-cohort clinical trial of Zolgensma (CL-101) and its extension study (START).²²

Overview of Trials

ENDEAR

ENDEAR included infants likely to be diagnosed with SMA Type I.¹⁷ Infants ≤ 7 months of age with two copies of *SMN2* who also showed clinical symptoms consistent with SMA at or before the age of six months were eligible for screening. Eligible infants were randomized 2:1 to receive either intrathecal Spinraza or sham injection. Randomization was stratified by disease duration (before or

after 12 weeks of disease); duration was determined by subtracting the age at symptom onset from the age at screening. Following randomization, participants received loading doses on study days 1, 15, 29, 64, and maintenance doses on study days 183 and 302. Spinraza was administered by lumbar puncture at a dosage adjusted to a dose equivalent to 12 mg in a child ≥ 2 years of age. Note this dosing differs slightly from the approved 12 mg dose for all patients.¹⁵ The sham injection was a small needle prick in the skin over the lumbar spine, covered with a bandage to resemble the Spinraza lumbar puncture. Parents of infants and trial personnel performing outcome assessments were blinded to treatment assignment, while trial personnel administering Spinraza and sham injections were aware of treatment assignment. As noted in Spinraza's label, more infants in the Spinraza group showed SMA symptoms before 12 weeks of age (88% vs. 77%), but the two treatment groups were otherwise balanced in baseline characteristics.¹⁵

ENDEAR's primary clinical outcomes were the proportion of HINE-2 ^a responders and event-free survival.¹⁷ HINE-2 responders were defined by meeting two criteria: score improvement in one or more categories **and** improvement in more motor milestone categories than worsening. Deaths and withdrawals were considered non-responses. Event-free survival was defined as death or permanent assisted ventilation, including tracheostomy or ventilation for ≥ 16 hours per day for 21 continuous days in the absence of an acute, reversible illness. Permanent assisted ventilation was adjudicated by an independent committee unaware of treatment assignments. Secondary outcomes relevant to our review included the proportion of CHOP-INTEND ^b responders, defined by a ≥ 4 -point change from baseline, overall survival, and event-free survival by disease duration sub-groups (≤ 12 vs. > 12 weeks).

An interim analysis comparing the proportion of HINE-2 responders was completed when 78 patients were followed for at least six months ("interim efficacy set": 27 sham control and 51 Spinraza patients; 43 patients were not yet followed for six months).¹⁷ This analysis showed statistical superiority of HINE-2 responders favoring Spinraza and the study was subsequently terminated prior to the planned 13-month follow up. All other endpoints were analyzed in the final analysis. Following early termination, participants could complete their end-of-trial (i.e., outcome assessment planned for day 394) visit at least two weeks after their most recent Spinraza dose or sham injection. The final efficacy set included 37 sham control and 73 Spinraza patients; 11 patients did not yet have the required visit at day 183 by the cut-off date for the final analysis. Safety analyses included all patients who were randomized and received at least one dose of their assigned treatment ("safety set," Spinraza: 80, sham: 41). Participants completing ENDEAR were eligible to enroll in the open-label extension trial, SHINE.

^aHINE-2 consists of eight items that assess incremental changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Higher scores indicate better functioning.

^bA validated 16-item scale (0–64 points) designed specifically to capture motor function in SMA infants with Type I. Higher scores indicate better functioning.

SHINE

SHINE is an ongoing Phase III OLE study that includes infants and children who completed ENDEAR and CHERISH, among other studies.²⁶ All participants receive Spinraza. Prior to FDA approval, Spinraza dosing followed the dosing used in ENDEAR and CHERISH (i.e., dosing scaled to a 12-mg equivalent for children under two and 12 mg for all other children); following FDA approval in 2016, all participants began to receive the 12-mg dose.²⁶ The key outcome of SHINE is to assess long-term safety including the incidence of AEs and SAEs. Of the infants from ENDEAR, 24/41 previously randomized to sham and 65/84 to Spinraza enrolled in SHINE and are now receiving Spinraza. Currently, results are only available for this subpopulation that were a part of the ENDEAR trial.

CS3A

CS3A is a Phase II, open-label, dose-escalation study. This study enrolled participants who showed symptoms consistent with SMA Type I between three weeks and six months of life.¹⁶ Eligible infants between three weeks and seven months of age were enrolled and received either 6 or 12 mg-equivalent doses (based on enrollment order) on study days 1, 15, 85, 253, and every four months thereafter. We report only data from the 16 participants who received 12 mg doses from study day 1 onward, as this regimen more closely aligns with the FDA label. Key outcomes relevant to this report included safety, HINE-2 scores and individual motor milestones of this tool, and CHOP-INTEND.

EMBRACE

EMBRACE was a two-part, randomized, sham-controlled, Phase II trial evaluating Spinraza in infants and children meeting any one of three criteria:²⁵

- Onset of clinical symptoms before six months of age and three *SMN2* copies
- Onset of clinical symptoms before six months of age, older than seven months of age, and have two *SMN2* copies
- Onset of clinical symptoms after six months of age, are 18 months of age or younger, and have two or three *SMN2* copies

Thirteen children in EMBRACE were diagnosed with infantile-onset SMA; data from these children are reported in the following section. Eight children were diagnosed with later-onset SMA; data pertaining to these children are reported in a later section (see “Later-Onset SMA”). Study enrollment, randomization, and the Spinraza dosing regimen were similar to ENDEAR and CHERISH. The primary outcome of part one was to assess Spinraza safety and tolerability in children ineligible to enroll (i.e., a more diverse population) in ENDEAR and CHERISH. Part one was terminated early following the ENDEAR interim analysis that demonstrated a statistically-significant benefit on HINE-2 response favoring Spinraza over standard care. Participants were subsequently able to enroll in

the EMBRACE open-label part two, in which all children received Spinraza. Data from this part of the study have not yet been reported.

Expanded Access Programs

We identified and included three prospective open-label cohort studies that evaluated clinical outcomes of patients receiving Spinraza prior to regulatory approval through EAPs.⁷³⁻⁷⁵ All patients were diagnosed with infantile-onset SMA and received age-adjusted doses of Spinraza through an EAP in Germany, Italy, or Australia. The Spinraza regimen was similar to the Spinraza label, with four loading doses on days 1, 15, 30, and 60 followed by maintenance doses every four months thereafter. Study eligibility was not restricted by *SMN2* copy number and the trial populations were generally more heterogeneous than the ENDEAR trial population (e.g., age at treatment initiation up to 35 years of age with 20 Italian patients older than 10 years). Key outcomes included changes in CHOP-INTEND, HINE-2, and ventilatory and nutritional support following six months of treatment.

CL-101 and START

CL-101 was a two-cohort Phase I study of Zolgensma in 15 symptomatic infants likely to develop Type I SMA.²² Infants with genetically-confirmed double-deletion of *SMN1* exon 7 and two copies of *SMN2* were eligible for inclusion. Infants were also screened for antibodies against the viral vector, AAV9, which would interfere with gene therapy using this vector; those with anti-AAV9 antibody titers >1:50 were excluded (n=1). Following screening, the first three patients received a single intravenous “low dose” of 6.7×10^{13} vector genomes (vg) per kilogram (kg); the next 12 patients received a single intravenous “high dose” of 2.0×10^{14} vg per kg. Due to elevated serum aminotransferase levels following dosing in the first patient, a protocol amendment added a prednisolone regimen of 1 mg/kg starting 24 hours before dosing through 30 days post-gene therapy administration. Concomitant treatment with Spinraza was not allowed during the 24 months of follow-up.

Treatment-related AEs of grade three or higher through the first two years following administration were CL-101’s primary outcome, and the time until death or permanent ventilatory support was the secondary outcome.²² Permanent ventilation was defined as 16 or more hours per day of ventilatory assistance for 14 or more days in the absence of an acute, reversible illness or perioperative state. Motor milestone achievements and CHOP-INTEND score changes through 13.6 months of age were measured as exploratory outcomes. Sitting unassisted was evaluated under three existing definitions: sitting unassisted for at least 5, 10, and 30 seconds. CHOP-INTEND scores were analyzed by a mixed-effects model for repeated measures, with the cohort and visit as a fixed effect and baseline CHOP-INTEND as a covariate. The use of nutritional and ventilatory support was also reported over time.

Infants were followed for two years, and data were reported by patient. One peer-reviewed publication included in our literature search reported data as of August 7, 2017, at which time all infants were 20 months of age or older.²² At this time, all three low-dose recipients and 7/12 high-dose recipients had the full 24 months of follow-up. Infants completing CL-101 were eligible for a long-term follow-up study (START), during which some patients received Spinraza treatment. A second publication included in our review reported early data from START.³²

Patient Characteristics

Key baseline characteristics of the populations enrolled in the two key trials, ENDEAR and CL-101, are shown in Table 3.1. We noted key differences at baseline with respect to age at diagnosis and age at treatment initiation which compromises the comparability of the two trial populations. Infants in ENDEAR were diagnosed later, on average, than those in CL-101 (Table 3.1).

Table 3.1. Key Baseline Characteristics of ENDEAR and CL-101

Key Characteristics	ENDEAR ¹⁷		CL-101 ²²	
	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
No. of Participants	80	41	3	12
Age at Onset, mo	1.8 (0.5-4.2)*	2.2 (0.2-4.6)*	1.7 (1.0-3.0)	1.4 (0-3.0)
Age at Diagnosis, wks	12.6 (0-29)	17.5 (2-30)	4.7 (0.6-12.1)†	8.6 (0-19.4)†
Disease Duration, wks	13.2 (0-25.9)	13.9 (0-23.1)	NR	NR
Age at Treatment Initiation, mo	5.4 (1.7-8.0)‡	6.0 (1.0-8.6)‡	6.3 (5.9-7.2)	3.4 (0.9-7.9)
Ventilatory Support, n (%)	21 (26)	6 (15)	3 (100)	2 (17)
Nutritional Support, n (%)	7 (9)	5 (12)	3 (100)	5 (42)
Mean HINE-2 Score	1.29 ± 1.07	1.54 ± 1.29	ND	ND
Mean CHOP-INTEND Score	26.63 ± 8.13	28.43 ± 7.56	16 (6-27)	28 (12-50)

Data are mean (range) or ±SD.

CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, HINE-2:

Hammersmith Infant Neurological Examination-Section 2, mo: months, ND: no data, NR: not reported, wks: weeks

*Converted from weeks to months by multiplying by 12 months and dividing by 52 weeks.

†Converted from days to weeks by dividing value by 7.

‡Converted from days to months by multiplying by 12 months and dividing by 365 days.

We also noted differences in baseline characteristics between the Spinraza and sham control arms of the ENDEAR trial (Table 3.1). In particular, there was a 4.8-week difference in mean age at diagnosis between the Spinraza and sham control arms and nearly 3-week difference in mean age at treatment initiation (163 days vs. 181 days for Spinraza and sham control, respectively).¹⁷ Compared to the sham control, infants randomized to Spinraza had a higher incidence of paradoxical breathing (where breathing movements occur in reverse of the normal chest wall movement, 89% vs. 66%), pneumonia and respiratory illness (35% vs. 22%), swallowing or feeding

difficulties (51% vs. 29%), and more commonly required ventilatory support (26% vs. 15%), suggesting more severe disease in the Spinraza arm.¹⁷ None of these differences were tested for statistical significance.

Most infants in the 12 mg Spinraza group in the CS3A study carried two copies of *SMN2* (n=13, 81%).¹⁶ Mean age at Spinraza initiation was considerably younger (mean age: 77 days, range: 15-130), and mean motor function was higher (mean HINE-2: 2 [1-12], mean CHOP-INTEND: 30 [17-74]) compared to infants enrolled in ENDEAR and START.

Three of four (75%) infants randomized to receive the sham control in EMBRACE and 3/9 (33%) randomized to Spinraza had two copies of *SMN2*. On average, children in the sham control group were older than those in the Spinraza arm (median age [range] at first dose: 25.6 [16-53] vs. 15.3 [7-49] months), however, the sample size was small.

In the German EAP, the 61 participants enrolled had either two *SMN2* copies (n=38, 62.3%) or three or more *SMN2* copies (n=20, 32.8%; missing data n=3) and were generally older than those enrolled in ENDEAR (mean age \pm SD at treatment initiation: 21.08 \pm 20.23). The mean (range) baseline CHOP-INTEND score was 22.3 (0-50), mean baseline HINE-2 score was 0.8 (0-8), and 55.8% of all children enrolled required nutritional support (i.e., feeding tube or gastrostomy). The primary outcome was mean change from baseline CHOP-INTEND at 60 and 180 days after initiating Spinraza treatment. CHOP-INTEND was assessed as the primary outcome; secondary outcomes included HINE-2 response and nutritional and ventilatory support. Drug dosing was the same as in SHINE (e.g., age-adjusted dosing for children under two years of age prior to approval and 12 mg for all children post-approval).

The Australian and Italian EAPs included similar participants, eligibility criteria, and outcomes as the German EAP.^{74,75} The 16 Australian participants started Spinraza treatment at a median (range) age of 20.0 months (2.5–35 years). The 104 Italian participants ranged in age from 0 to 19 years old.

Survival

In ENDEAR, the Spinraza group showed a 63% lower risk of death versus the sham control (hazard ratio [HR] [95% CI]: 0.37 [0.18, 0.77], p=0.004).¹⁷ Overall, mortality was lower in infants in the Spinraza group versus the sham control group (16% vs. 39%). In a prespecified subgroup analysis, Spinraza demonstrated a statistically-significant survival benefit over the sham control (standard care) for children who initiated treatment within 12 weeks of disease onset (HR: 0.22 [NR], p=0.03).⁷⁶ A statistically significant benefit was not demonstrated for children initiating Spinraza treatment more than 12 weeks after symptom onset (HR: 0.45 [NR], p=0.09)).

Three of 16 (19%) infants in the CS3A 12-mg group died during study follow-up: one due to SMA disease progression and two due to recent pulmonary infection.¹⁶

All infants treated with Zolgensma in CL-101 were alive at 20 months of age, per results reported at a data cut-off of August 7, 2017.²² All 12 patients followed in START (mean post-treatment age: 39 months) were alive.²³

Permanent Ventilatory Support

In ENDEAR, there was no statistically-significant difference between the Spinraza and sham control groups in avoiding permanent ventilatory support: at the end of the trial, 62/80 (78%) and 28/41 (68%) of infants did not require permanent assisted ventilation (HR [95% CI]: 0.66 [0.32, 1.37]).¹⁷ Compared to baseline, a smaller proportion of Spinraza recipients required ventilatory support at the final analysis while more sham control infants required ventilation versus baseline (Table 3.2).

Prespecified subgroup analysis showed statistically-significant benefits on ventilation-free survival favoring Spinraza over standard care for infants initiating treatment within 12 weeks of disease onset (HR [95% CI]: 0.158 [NR], $p < 0.004$). Analyses of patients with disease duration less than or equal to the group median (13.1 weeks) showed similar results. A statistically significant benefits on ventilation-free survival were not demonstrated for children who initiated Spinraza more than 12 weeks after symptom onset (HR [95% CI]: 0.816 [NR], $p = 0.5$).

Table 3.2. Ventilatory Support in ENDEAR and START

	ENDEAR ^{17*}		CL-101 ^{22†}	
	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
Follow-Up	Final analysis		Interim analysis	
No. of Participants	80	41	3	12
Baseline Ventilation Support	21 (26)	6 (15)	3 (100)	2 (17)
Post-Treatment Ventilation Support	18 (22.5)	13 (32)	NR	5 (42)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.

NR: not reported

*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.

†24 month follow-up.

None of the infants in the 12 mg group in the CS3A study required permanent ventilation during study follow-up.¹⁶

Nineteen (31%) of German EAP participants were ventilator-free after six months of Spinraza treatment and four (7%) children reported decreased use of ventilatory support.⁷³ Six (10%) participants began noninvasive ventilation for less than 16 hours per day, four (7%) children

required noninvasive ventilation for more than 16 hours per day, and three (5%) children underwent tracheostomy.

One patient in the CL-101 cohort 1 qualified as needing permanent ventilatory support per the protocol definition but later required only 15 hours per day of ventilatory support following a salivary gland ligation operation.²² This event was not included in the analysis of event-free survival.

Event-Free Survival

Spinraza demonstrated a statistically-significant 47% decrease in the risk of death or permanent assisted ventilation (HR [95% CI]: 0.53 [0.32, 0.89], $p=0.005$); 49/80 (61%) of Spinraza and 13/41 (32%) of sham control recipients avoided death and permanent ventilatory support.¹⁷ In the sham control group, the median time to death or permanent assisted ventilation was 22.6 weeks, whereas the Spinraza group had not reached this endpoint by the end of the trial. Interim long-term follow-up data from SHINE show the median time to death or permanent ventilation for infants who received Spinraza in ENDEAR and SHINE was 73.0 (95% CI: 36.3, NA) weeks.²⁶

Seven infants in the CS3A study died or required permanent ventilation; because most infants in CS3A were alive and without permanent ventilation, the median age of event-free survival was not reached.¹⁶

None of the participants of the Australian EAP died or required ventilation for 16 or more hours per day after a median treatment period of 5.1 months.⁷⁵

All infants treated with Zolgensma in CL-101 were alive and event-free through 24 months of follow-up.^{22,27} As described above, one patient in the low-dose cohort met criteria for permanent ventilatory support but later improved; this patient was considered event-free.

Motor Function and Milestones

HINE-2

HINE-2 response was the primary outcome in ENDEAR (Table 3.3).^{17,22} Key motor or developmental milestones evaluated in the HINE-2 included head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. To meet responder criteria, infants had to improve in one or more milestones and show more milestones with improvement than worsening. Infants who received Spinraza in ENDEAR showed statistically-significant improvements in HINE-2 response compared to sham control at the interim analysis (21/51 [41%] of Spinraza and 0/27 of sham control group; $p<0.001$).¹⁷ In the final analysis, 37/73 (51%) of Spinraza and 0/37 sham control patients met criteria for HINE-2 response. On average, infants who received Spinraza through study day 394 ($n=26$) gained a mean 5.9 (min, max: 4.9, 6.9) milestones compared to sham control infants

(n=11), who showed minimal changes in HINE-2 motor milestones (mean [min, max]: -0.2 [-0.9, -0.4]). Nearly twice as many infants with SMA disease duration ≤12 weeks met HINE-2 responder criteria compared to infants with disease duration of more than 12 weeks (75% vs. 32%).⁷⁶

The EMBRACE and CS3A studies show similarly high proportions of HINE-2 responders among small sample sizes. Seven of nine (78%) of infants with infantile-onset SMA in EMBRACE met criteria as HINE-2 responders based upon the last available assessment for each child (day 183, 304 or 422).²⁸ None of the children randomized to receive the sham control met any of the milestones assessed in the HINE-2. Thirteen of 15 (87%) children with SMA Type I in the CS3A study met identical criteria as HINE-2 responders.¹⁶

Table 3.3. HINE-2 Results for Spinraza in Infantile-Onset (Type I) SMA

	ENDEAR ¹⁷		EMBRACE ²⁸	
Treatment	Spinraza	Sham Control	Spinraza	Sham Control
Assessment Timepoint	Day 183		14 months	
No. of Participants	59	23	9	4
Mean Baseline Score, Points	1.29 ± 1.07	1.54 ± 1.29	NR	NR
Mean Change from Baseline, Points	2.4 (2.8, 3.1) *	0 (-0.3, 0.3) *	NR	NR
Mean Score at Follow-Up, Points	NR	NR	NR	NR
Responder†, n (%)	21 (41)‡	0§	7 (78)	0

Data are mean (min, max) or ±SD.

HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported

*Data estimated from publication by ICER.

†Responder defined as meeting two criteria: score improvement in one or more categories and improvement in more motor milestone categories than worsening.

‡Based on interim data analysis. Denominators were 51 for Spinraza and 27 for sham control.

Under identical HINE-2 responder criteria, 21 (34.4%) of children in the German EAP demonstrated motor response (mean change from baseline: 1.4 ± 2.1).⁷³ Italian patients, which included eight infants as well as patients aged 2, 5, 7, 9, 12, 14, and 35 years old, showed similar improvements in HINE-2 scores (mean change from baseline: 1.3 ± 2.2).⁷⁴ The Australian EAP did not report HINE-2 data.

CL-101 did not collect HINE-2 data, and there are no published data reporting HINE-2 scores with Zolgensma treatment.

CHOP-INTEND

CHOP-INTEND results from ENDEAR (secondary) and CL-101 (exploratory) are shown in Table 3.4. There is no minimal clinically-important difference (MCID) defined in the literature, however, a 4-point change is considered an important change in CHOP-INTEND response across trials for both

Spinraza and Zolgensma. In general, the literature cites a 40-point threshold as indicating clinically-meaningful function; it is rare for infants with Type I SMA to have a score of 40 or more points on the CHOP-INTEND.^{30,31} Briefly, CHOP-INTEND assesses 16 motor skills, such as hand grip, rolling, and head control. Each motor skill is scored from 0 (no response) to 4 (complete response); a response of 4 points may reflect complete response in head control, or slight improvement across hand grip, rolling, and head control, among other motor skills. On average, healthy infants aged three months have a CHOP-INTEND score (range) of 50.1 (32-62) while similarly aged infants with SMA have an average score of 20.2 (10-33) points.²⁹

In ENDEAR, 71% of infants treated with Spinraza achieved an increase of ≥ 4 points in CHOP-INTEND score between baseline and their end-of-trial visit (Table 3.4); only one infant in the sham control arm achieved improvement.¹⁷ Decreases in CHOP-INTEND scores were reported in far fewer infants who received Spinraza compared to the sham control (7% vs. 49%).¹⁷

Infants treated with the high dose of Zolgensma (cohort 2) in the CL-101 trial showed improvement in CHOP-INTEND scores at one- and three-months post-treatment with Zolgensma (9.8 and 15.4 points, respectively).²² CHOP-INTEND scores through the data cut-off for the preliminary analysis showed slight increases for the low-dose cohort (Table 3.4), however, all three patients remained below the threshold of ≥ 40 points that indicates clinically-meaningful function. Cohort 2 showed marked improvement in score (Table 3.4); 11 of 12 infants achieved and maintained a CHOP-INTEND score of ≥ 40 points at a median age of 20 months.

Table 3.4. CHOP-INTEND Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR ¹⁷		CS3A ¹⁶	CL-101 ²²	
Follow-Up	Final analysis*		18 months	Interim analysis†	
Treatment	Spinraza	Sham control	Spinraza	Zolgensma, Cohort 1	Zolgensma, Cohort 2
No. of Participants	73	37	14	3	12
Mean Baseline Score, Points	26.63 \pm 8.13	28.43 \pm 7.56	30 (17-64)	16.3 (6-27)	28.2 (12-50)
Change from Baseline, Points	NR	NR	15.2	7.7	24.6
Responder‡, n (%)	52 (71)	1 (3)	12 (86)	NR	NR

Data are mean (range) or \pm SD. Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.

CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, NR: not reported

*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.

†Data cut-off at August 7, 2017. 3/3 and 7/12 patients had 24 months of follow-up.

‡Responder defined as achieving ≥ 4 -point increase in CHOP-INTEND score.

Twelve of 14 (86%) infants in the dose-ranging CS3A study who received 12 mg doses of Spinraza improved by an average 15.2 ($p=0.0013$) points from baseline in CHOP-INTEND (Table 3.4).¹⁶ The number of infants reaching the clinical threshold of 40 points on the CHOP-INTEND increased from no children at baseline to 7/13 (54%) infants with two *SMN2* copies in the 12 mg group.

Two of the three included EAPs reported CHOP-INTEND results. Data from the German EAP showed a mean \pm standard deviation CHOP-INTEND improvement of 9.0 ± 8.0 points, for a total score of 31.2 ± 16.2 after six months of treatment.⁷³ Thirteen percent of children achieved a CHOP-INTEND improvement of 4 or less points; 54% showed an improvement of 5 to 14 points, and 18% improved by 18 or more points. Despite having lower CHOP-INTEND scores at baseline, children with two copies of *SMN2* achieved similar motor function gains after treatment compared to children with three *SMN2* copies (8.1 ± 7.0 vs. 8.2 ± 5.3). The study observed an age-related treatment effect on change from baseline CHOP-INTEND, where children seven months and younger improved more than children older than seven months (14.4 ± 9.2 vs. 7.0 ± 6.6 , respectively). Subsequent univariate analysis demonstrated that the age at treatment initiation was correlated with change in CHOP-INTEND.

Italian EAP participants improved by a mean 19.6 ± 16.4 points from baseline CHOP-INTEND ($p<0.001$ for baseline vs. six-month score). Improvements from baseline CHOP-INTEND were statistically significant ($p<0.001$) regardless of *SMN2* copy number. Twenty of the 71 patients (28%) older than two years and six of 20 patients (30%) older than 10 years demonstrated an improvement of ≥ 4 points from baseline CHOP-INTEND.

Motor Milestones

Motor milestones achieved in ENDEAR and CL-101 are shown in Table 3.5. A majority of infants who received Zolgensma achieved head control and rolling over and a minority of infants who received Spinraza achieved head control, rolling over, sitting assisted, or standing with assistance (Table 3.5). Data from the CL-101 trial showed 11 of 12 (92%) children in cohort 2 treated with Zolgensma were able to sit unassisted for ≥ 5 seconds, 10 (83%) for at least 10 seconds, and 9 (75%) for at least 30 seconds at the end of the two-year trial follow-up.²² Two more children also achieved sitting unassisted for 30 or more seconds during additional follow-up past two years.³² Nine (75%) children achieved rolling and 2 (17%) achieved crawling, pulling to stand, standing, and walking independently during CL-101 two-year follow-up.²² Two more children achieved standing with support in the additional follow-up in START (4/12 [33%] in total).³²

Table 3.5. Motor Milestone Results for Spinraza and Zolgensma in Infantile-Onset (Type I)

Other Motor Milestones	ENDEAR ^{17*}		CL-101 ^{22†}	
	Spinraza N=73	Sham Control N=37	Zolgensma, Cohort 1 N=3	Zolgensma, Cohort 2 N=12
Head Control	16 (22)	0	NR	11 (92)
Roll Over	7 (10)	0	NR	9 (75)
Sitting Unassisted	6 (8)‡	0‡	NR	10 (83) [§]
Standing with Assistance	1 (1)	0	NR	2 (17)
Standing Independently	NR	NR	NR	2 (17)
Walking Independently	NR	NR	NR	2 (17)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.

HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported

*The HINE-2 motor milestone achievements of infants at the later of days 183, 302, and 394. Infants with opportunity for at least a 6-month assessment were included.

†24 month follow-up.

‡Includes “stable sit” and “pivots” from HINE-2.

§Sitting unassisted for at least 10 seconds is in accordance with WHO Motor Milestones criteria.

Long-term follow-up data from SHINE shows additional motor milestone achievements for infants who transitioned from ENDEAR to SHINE. Data from the interim analysis (June 15, 2017) are presented in Table 3.6.²⁶

Table 3.6. ENDEAR to SHINE Motor Milestone Achievements²⁶

	Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
No. with Available Data	81	70	65	51	48	31	17
% Achieved Full Head Control	0	7	17	25	33	45	35
% Achieved Independent Sitting	0	1	5	10	15	29	24

Data are from children who received Spinraza in ENDEAR and SHINE.

In EMBRACE, none of the children who randomized to receive the sham control met any of the milestones assessed in the HINE-2; four (44%) children achieved improvements in head control, six (67%) in rolling, and five (56%) in sitting.²⁸ None of the children with infantile-onset in the study showed improvements in crawling, standing, or walking.

After six months of Spinraza, children in the Italian and German EAPs achieved one less motor milestone compared to infants who received Spinraza in ENDEAR.^{73,74} Four German children (7%) achieved full head control, two (3%) could sit independently, however, none of the children achieved independent standing or walking.⁷³

Other Outcomes

Bulbar Function and Nutritional Support

Twenty-four months after treatment with Zolgensma, 11 (92%) CL-101 patients treated in cohort 2 were able to swallow safely, enabling oral feeding (vs. four at baseline).³² The same 11 patients were able to speak. Additional follow-up in START showed sustained swallowing which enabled oral feeding in all 10 patients followed. Two of these patients received Spinraza during this extension study.²³ Finally, we found limited data regarding post-treatment nutritional support in both the CL-101 and ENDEAR trials (e.g., gastrointestinal tubes) (Table 3.7).

Following six months of Spinraza treatment, 39% of German EAP participants were free of nutritional support via gastronomy tube; five children (8%) required nutritional support during Spinraza treatment.⁷³ Three Italian EAP participants required nutritional support during Spinraza treatment; all three patients had two copies of *SMN2*, disease onset before three months of age, and were diagnosed prior to the start of the EAP.⁷⁴

Table 3.7. Nutritional Support Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR ¹⁷		CL-101 ^{22,32}	
	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
Follow-Up	Final analysis*		Final analysis†	
No. of Participants	80	41	3	12
Baseline GI Tube Use	7 (9)	5 (12)	3 (100)	5 (42)
Post-Treatment GI Tube Use	NR	NR	NR	6 (50) ‡

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.

GI: gastrointestinal, NR: not reported

*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.

†24 month follow-up.

‡Of five patients requiring tube at baseline, four were able to feed orally and 11/12 were able to swallow independently at last follow-up.

Later-Onset (Type II and III) SMA

One sham-controlled RCT (CHERISH) reported on outcomes of Spinraza in children ages two to 12 years with later-onset SMA (Types II and III), and one Phase Ib/IIa open-label, dose-ranging study (CS2/CS12) on outcomes in children ages two through 15.^{18,28} EMBRACE reported on eight children diagnosed with later-onset SMA with broader inclusion criteria than that of CHERISH. Two

prospective cohort studies reported on Spinraza in ambulatory and non-ambulatory adolescents and adults. We did not identify any trials assessing Zolgensma in this population.

Overview of Trials

CHERISH

CHERISH is a sham-controlled RCT which evaluated the safety and efficacy of Spinraza in children two through 12 years old who developed SMA symptoms after six months of age.¹⁷ Children scoring between 10 and 54 points on the Hammersmith Functional Motor Scale-Expanded (HFMSE)^c who were able to sit unassisted but unable to walk independently were eligible for screening. Children with severe scoliosis and those requiring ventilatory support, defined as requiring invasive or non-invasive support for greater than six hours per day, or gastric tubes for nutritional support were excluded. Eligible children were randomized 2:1—stratified by age (<6 vs. ≥6 years old)—to receive either Spinraza or sham injections on study days 1, 29, 85, and 274, which differs from the approved administration schedule of loading doses on days 1, 15, 29, and 59, followed by maintenance doses every four months thereafter. Spinraza doses were 12 mg delivered by lumbar puncture. The sham injection procedure and study blinding were similar to that described above for ENDEAR, with the addition that children were sedated during their treatment procedure.

CHERISH's primary outcome was the least-squares mean change from baseline in HFMSE score after 15 months of treatment, with a threshold of three points considered clinically meaningful.¹⁷ The proportion of children with an increase of three or more points in HFMSE between baseline and 15 months was a secondary outcome, along with the proportion of children achieving one or more new WHO motor milestones and the change from baseline in the RULM^d score.

The sponsor conducted a prespecified interim analysis of the primary outcome when all children had been enrolled for a minimum of six months **and** 39 or more children had completed 15-month evaluations.¹⁷ At the time of interim analysis, 54 children (43%) had completed their 15-month evaluation; for the 72 children (57%) who had not yet reached the 15-month assessment, multiple imputation was used to account for HFMSE scores for children with shorter follow-up. Results of the interim analysis showed a statistically-significant benefit on HFMSE score favoring Spinraza, and the trial was terminated early. Like the ENDEAR study, children were invited to complete the 15-month assessment at this time and were eligible to enroll in SHINE to receive Spinraza. The final analysis included all outcomes; however, the primary outcome was not tested statistically a second time. At the time of final analysis, 100 children (79%) had completed their 15-month evaluation; for

^c A clinician-rated, 20-item scale developed to assess the motor ability of children with SMA with limited ambulation. Higher scores indicate better functioning. Patients and caregivers consider a 1-point increase meaningful.

^d An assessment designed for upper limb function in patients with SMA. Higher scores indicate better functioning.

the 26 children (21%) who had not yet reached the 15-month assessment, multiple imputation was used for three outcomes (change from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and change from baseline in the RULM score).

CS2/CS12

CS2 was a multiple-dose, open-label study followed by its open-label extension study, CS12. CS2 included four cohorts of children which received one of four doses – 3, 6, 9, or 12 mg – on the same regimen as CHERISH (study days 1, 29, and 85).²⁸ The first two cohorts each included eight children and the second two cohorts each included nine children (n=34). Children were followed for six months after the last day of treatment (day 85). The subsequent CS12 study enrolled children from CS2 as well as other eligible children. The enrolled children could receive four doses of Spinraza on CS12 study days 1, 169, 351, and 533; participants rolling over from CS2 received a total of eight doses through day 533 of CS12. Children were followed for six months following the day 533 dose. The primary outcome of these two studies was safety and tolerability of Spinraza lumbar punctures. Exploratory outcomes included the HFMSE, ULM in non-ambulatory children, and 6MWT ^e for ambulatory children.

EMBRACE

As described in the infantile-onset section, EMBRACE was a two-part Phase II trial evaluating Spinraza in a broader population of infants and children compared to ENDEAR.²⁵ Eight children were diagnosed with later-onset SMA; relevant data are summarized below. Study enrollment, randomization, and the Spinraza dosing regimen were similar to ENDEAR and CHERISH. The primary outcome of part one was to assess Spinraza safety and tolerability in children ineligible to enroll (i.e., a more diverse population) in ENDEAR and CHERISH.

Prospective Cohort Studies

Ambulatory and non-ambulatory patients with later-onset SMA received Spinraza in two prospective cohort studies.^{77,78} Stolte et al., treated 28 adults (nine with Type II and 19 with Type III) ages 18-61 with nusinersen, and Wurster et al., treated 20 adolescents and adults (nine with Type II and 11 with Type III). Inclusion criteria for both studies were less restrictive compared to CHERISH and EMBRACE (e.g., did not exclude participants with scoliosis or spine fusion surgeries⁷⁸ or nonambulatory participants.⁷⁷)

Patient Characteristics and Follow-up

Baseline characteristics of children who participated in CHERISH are presented in Table 3.8. The Spinraza and sham control groups were well-balanced regarding the age at diagnosis and overall

^e A measure of ambulatory function, specifically how far an individual can walk within six minutes.

motor function and milestones. Children in the Spinraza group appeared to be older with a longer duration of SMA symptoms compared to the sham control group (Table 3.8). There were also fewer children able to walk in the Spinraza group than in the sham control.¹⁸

Table 3.8. Key Baseline Characteristics of CHERISH

Baseline Characteristic	CHERISH ¹⁸	
	Spinraza	Sham Control
No. of Participants	84	42
Age at Onset, mo	10.0 (6-20)	11 (6-20)
Age at Diagnosis, mo	18.0 (0-48)	18 (0-46)
Disease Duration, mo	39.3 (8-94)	30.2 (10-80)
Age at Screening, yr	4.0 (2-9)	3.0 (2-7)
Mean HFMSE Score	22.4 ±8.3	19.9 ±7.2
RULM Score	19.4 ±6.2	18.4 ±5.7
Ability to Sit Without Support*	84 (100)	42 (100)
Ability to Walk Without Support*	20 (24)	14 (33)
Ability to Walk Independently*, ≥15m	0	0

Data are mean (range) or ±SD.

HFMSE: Hammersmith Functional Motor Scale-Expanded, mo: months, NR: not reported, RULM: Revised Upper Limb Module, yr: years

*Motor milestone ever achieved. Data are n (%).

Similar proportions of patients in the two treatment groups completed the end-of-study visit (79% vs. 81%) or were followed through the study termination (21% and 19%).¹⁸ Discontinuation of study participation was also similar between groups, with only one child in the Spinraza group discontinuing participation due to early study termination.

Children enrolled in the CS2 study were generally older than children in CHERISH (mean age [SD]: 7.0 years [4.0]).²⁸ These children were, on average, diagnosed later in life compared to those in CHERISH, however, there was a large difference in age at diagnosis in CS2 where children with Type II were diagnosed much younger than those with Type III (15.4 [6.3] vs. 43.6 [32.4]). Most children (75%) in the study had two copies of *SMN2*, and approximately half were able to walk. All children could sit without assistance, 61% could walk with assistance, 43% could stand unassisted, and 46% could walk independently.

Children diagnosed with later-onset SMA in EMBRACE (n=8) were generally younger than children in CHERISH; the median age (range) at the first dose for the Spinraza and sham control arms were 18.1 (16-19) months and 17.0 (15-19) months, respectively. All five of the Spinraza recipients and two of three sham control recipients had three copies of *SMN2*, while the remaining sham control recipient had only two copies of *SMN2*.

The mean age for participants of the prospective cohort studies were notable older. For adults with Type II and III SMA in the Stolte et al. study, mean age at first dose of Spinraza was 31.2 years (range: 24-48) and 37.9 (range: 18-61), respectively.⁷⁷ About half of adults with Type III were able to walk, and none of those with Type II could walk at treatment initiation and baseline RULM scores reflected this split (mean \pm SD: 9.9 ± 4.6 and 29.5 ± 8.5 for Types II and III, respectively). HFMSE scores similarly reflected differences in functional motor abilities between Types II and III (mean \pm SD: 3.1 ± 2.5 and 31.2 ± 18.1 , respectively). Participants in the Wurster et al. study were ages 11-60. The nine participants with SMA Type II and 11 with Type III had a mean HFMSE score of 1.7 (SD: 2.2) and 30.1 (25.0).⁷⁸ Baseline RULM scores were not reported.

Survival

Survival was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies. There were no deaths during either of these studies.

Permanent Ventilatory Support

Permanent ventilation was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies, and no data on permanent ventilation were available.

Event-Free Survival

Event-free survival was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies, and no data on event-free survival were available.

Motor Function and Milestones

HFMSE

Spinraza demonstrated a statistically-superior least-squares mean increase from baseline HFMSE score after 15 months of treatment compared to the sham control at the interim analysis (Table 3.9), leading to early study termination.¹⁸ As described previously, the CHERISH interim analysis used the multiple imputation method to account for data missing from children who had not yet completed the 15-month assessment. This analysis included 15-month data from 39 Spinraza and 19 sham control recipients, which is 43% of the enrolled population; data for the remaining 45 Spinraza and 23 sham control recipients were imputed.

For the final analysis, HFMSE data from 18 Spinraza and eight sham control recipients were imputed, as these children still had not yet completed the 15-month assessment. With fewer data imputed, results from the final analysis of mean increase from baseline HFMSE showed a smaller treatment difference than in the interim analysis, although the results remained favorable to Spinraza (mean difference [95% CI]: 4.9 [3.1, 6.7], Table 3.9).¹⁸ A greater proportion of children

who received Spinraza showed a response of ≥ 3 -point increase in HFMSE score versus the sham control, and the calculated odds ratio favored Spinraza treatment over sham control (odds ratio [OR] [95% CI]: 6 [2-15]).

Participants in the Stolte et al. study with Types II and III showed stable HFMSE scores after four doses of Spinraza compared to baseline scores (Type II: 2.0 ± 2.5 vs. 9.9 ± 4.6 , $p=0.6$; Type III: 30.8 ± 24.8 vs. 31.2 ± 18.1 , $p=0.3$). EMBRACE and Wurster et al. did not report post-treatment HFMSE data.

Table 3.9. HFMSE Results from CHERISH in Later-Onset (Type II/III) SMA

CHERISH ¹⁸			
	Spinraza* N=84	Sham Control* N=42	Treatment Difference†
Interim Analysis			
n (%) with 15-Month Data	35 (42)	19 (45)	--
n (%) with HMFSE Data Imputed	49 (58)	23 (55)	--
HFMSE‡ Change from Baseline	4.0 (2.9-5.1)	-1.9 (-3.8-0)	5.9 (3.7, 8.1)
Final Analysis			
n (%) with 15-Month Data	66 (79)	34 (81)	--
n (%) with HFMSE Data Imputed	18 (21)	8 (19)	--
HFMSE‡ Change from Baseline	3.9 (3.0-4.9)	-1.0 (-2.5-5.0)	4.9 (3.1, 6.7)
% of HFMSE Responders§	57 (46-68)	26 (12-40)	OR: 6 (2, 15)

HFMSE: Hammersmith Functional Motor Scale-Expanded, OR: odds ratio

*Data are mean (min-max) or n (%).

†Data are the difference in treatment with Spinraza vs. sham (95% CI).

‡Least-squares mean change from baseline.

§Defined as change from baseline of ≥ 3 points.

Upper Limb Function

In CHERISH, upper limb motor function, as measured with RULM, improved with Spinraza treatment (least-squares mean score [95% CI]: $4.2 [3.4, 5.0]$) and remained stable in the sham control group ($0.5 [-0.6, 1.6]$).¹⁸ The treatment difference for RULM score ($3.7 [2.3, 5.0]$) was not formally tested for statistical significance.

In CS2/CS12, at study day 253, 9/11 (82%) and 3/16 (19%) SMA Type II and III children improved by ≥ 3 points from baseline HFMSE.²⁸ All six Type III children followed through day 1,050 showed the same improvement; however, only 2/7 (29%) Type II children met the same clinical threshold. Four of six (67%) children with Type II SMA followed through day 1,050 demonstrated clinically-meaningful improvement (≥ 2 points) in upper limb motor function, as assessed by ULM. Motor function of all children ($n=6$) with Type III improved, based on the clinically-meaningful threshold for the 6MWT (gain of ≥ 30 meters).

Motor Milestones

New achievements in walking with assistance, standing alone, and any WHO motor milestone were reported by similar proportions of Spinraza and sham control groups (Table 3.10). Note these data were analyzed only among the children who had completed the 15-month assessment (i.e., no data were imputed). One child in each group gained the ability to stand alone, and one child in the Spinraza group achieved walking with assistance.¹⁸

Table 3.10. Motor Milestone Results for Spinraza in Later-Onset (Type II/III) SMA

	CHERISH ¹⁸		EMBRACE ³⁶	
	Spinraza* N=84	Sham Control* N=42	Spinraza N=5	Sham Control N=3
Assessment Timepoint	Final Analysis		Final Analysis†	
N (%) Analyzed	66 (79)	34 (81)	5 (100)	3 (100)
% Who Achieved New WHO Motor Milestone	20 (11-31)	6 (1-20)	NR	NR
Sitting, n (%)	NR	NR	4 (80)	1 (33)
Crawling, n (%)	NR	NR	3 (60)	1 (33)
Standing, n (%)	1 (2) ‡	1 (3) ‡	2 (40) §	2 (67) §
Walking, n (%)	1 (2) ‡	0 (0) ‡	1 (20) §	0 §

NR: not reported, WHO: World Health Organization

*Data are mean (min-max) or n (%).

†Individuals with 6 month (day 183), 10 month (day 304), and 14 month (day 422) visit included. The last assessment available was used for this analysis.

‡Per WHO motor development milestones definition.

§Per HINE-2 definition.

Presymptomatic SMA

One single-arm trial included in our systematic literature review, NURTURE, reported on Spinraza treatment in presymptomatic infants. Trials of Zolgensma are ongoing and no data have been presented to date.

Overview of Trial

NURTURE

NURTURE is a Phase II, single-arm, open-label, multi-center trial of presymptomatic infants. To be eligible for NURTURE, infants were required to be six weeks of age or less, have a documented genetic diagnosis of SMA, and have two or three copies of *SMN2* (i.e., infants most likely to develop SMA Type I or II).⁷⁹ Infants showing any signs or symptoms suggestive of SMA onset were excluded. Twenty-five infants were enrolled and will be followed through January 2022 to evaluate the

primary outcome of time to death or respiratory intervention. Respiratory intervention is defined as invasive or non-invasive ventilation for six or more hours a day for seven days or longer or tracheostomy. Secondary outcomes include: the proportion of infants manifesting SMA symptoms, survival, HINE and WHO motor milestones, CHOP-INTEND, HFMSE, and AEs.

Patient Characteristics and Follow-up

Data are reported by *SMN2* subgroup; having two copies of *SMN2* is predictive of later developing SMA Type I, and three copies is predictive of SMA Type II. Most infants received their first dose within the first 28 days of life (Table 3.11). Baseline CHOP-INTEND scores were slightly lower in infants with two *SMN2* copies than those with three *SMN2* copies. The most recent interim analysis was completed in May 2018, at which time the median age at the most recent visit was 26.0 months (range: 14.0-34.3), and median time on treatment was 27.1 months (15.1-35.5).

Table 3.11. Key Baseline Characteristics from NURTURE

Baseline Characteristics		2 <i>SMN2</i> Copies	3 <i>SMN2</i> Copies	All Participants
No. of Participants		15	10	25
Age at First Dose, Days	≤14	6 (40)	3 (30)	9 (36)
	>14 and ≤28	7 (47)	5 (50)	12 (48)
	>28	2 (13)	2 (20)	4 (16)
	Median	19.0 (8-41)	23.0 (3-42)	22.0 (3-42)
Females		7 (47)	6 (60)	13 (52)
CHOP-INTEND Score		45.0 (25.0-60.0)	53.5 (40.0-60.0)	50.0 (25.0-60.0)
HINE Total Milestones		3.0 (0-5.0)	3.0 (0-7)	3.0 (0-7)

Data are n (%) or median (range).

Survival and Permanent Ventilatory Support

In NURTURE, all 25 children treated with Spinraza were alive at the May 2018 interim analysis. Four (16%) children met the primary outcome of required respiratory intervention (defined as requiring six or more hours per day for seven consecutive days or tracheostomy); all four children had two *SMN2* copies. All of these infants received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy.

Motor Function and Milestones

Interim data from July 2017 evaluated whether children participating in NURTURE showed any protocol-defined symptoms of SMA by 13 months of age. A total of 17 children had analyzable data from the Day 365 study visit, of whom 8/12 (67%) and 1/5 (20%) children with two and three *SMN2* copies, respectively, had developed one or more SMA symptoms. None of these nine children achieved hands and knees crawling (average age of attainment: 8.5 months). Five of 12 (42%) children with two *SMN2* copies were unable to stand with assistance (average age of attainment:

9.2 months; Table 3.12). It is equally common for infants to achieve hands-and-knees crawling before standing with assistance as it is to achieve standing with assistance before hands-and-knees crawling.⁵⁵

By the May 2018 interim analysis, caregivers reported all 25 (100%) children had achieved sitting without support, 22/25 (88%) of children had achieved walking with assistance, and 17/25 (68%) had achieved walking alone (Table 3.12). Four children each achieved sitting unsupported and walking alone later than expected in healthy children, and seven children were able to walk with assistance later than expected. At the most recent study visit, the mean (range) CHOP-INTEND scores for children with two and three *SMN2* copies were similar and reflected near-maximal motor function (two copies: 61.0 [46-64]; three copies: 62.6 [8-64]).

Table 3.12. WHO Motor Milestone Achievements for Spinraza in Presymptomatic SMA

WHO Motor Milestone	Expected Age Range of Attainment*	July 2017†‡		May 2018†§	
		2 <i>SMN2</i> Copies	3 <i>SMN2</i> Copies	2 <i>SMN2</i> Copies	3 <i>SMN2</i> Copies
Independent Sitting	3.8 – 9.2	14 (93)	8 (80)	15 (100)	10 (100)
Walking with Assistance	5.9 – 13.7	5 (33)	7 (70)	12 (80)	10 (100)
Walking Alone	8.2 -17.6	3 (20)	5 (50)	8 (53)	9 (90)

*Data reported in months. Range defined by 1st-99th percentile for the windows of milestone achievement.

†Data reported as N (%).

‡The median age at the most recent visit was 14.7 months (range: 2.8-23.3).

§The median age at the most recent visit was 26.0 months (range: 14.3-34.3).

All Populations: Harms

Safety data were collected in four clinical trials of Spinraza (ENDEAR, CHERISH, EMBRACE, and SHINE) and Zolgensma (CL-101/START). Integrated safety data from the Spinraza trials and CL-101/START are presented in Table 3.13.

Sixteen percent of infants who received Spinraza and 39% of sham control infants in ENDEAR discontinued study participation due to AEs (Table 3.13).¹⁷ No children in CHERISH or NURTURE discontinued due to AEs.^{18,37} Treatment-related AEs were rare in all Spinraza trials (Table 3.13). SAEs were more frequently reported by sham control than Spinraza recipients in ENDEAR (95% vs. 76%, respectively) and CHERISH (29% vs. 17%, respectively).^{17,18}

We noted differences in AEs related to the route of administration. Many of the frequently-reported AEs reported following treatment with Spinraza were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain). Lumbar-puncture-associated AEs were reported only by children in CHERISH; however, this is likely due to the difficulty of collecting information from infants. Additional common AEs associated with Spinraza include: lower

respiratory tract infection and constipation (Table 3.13). Fever was more common among infants (ENDEAR) than older children (CHERISH) compared to the sham control.

Based on clinical trial data and known side-effects related to oligonucleotides with a phosphorothioate backbones,³⁸ two safety concerns are highlighted in the Spinraza prescribing information: risk of thrombocytopenia and potential for kidney damage (renal toxicity).¹⁵ FDA-required monitoring to assess patient safety includes coagulation and quantitative spot urine testing prior to each dose.

Table 3.13. Harms Reported in START and Spinraza Clinical Trials

	CL-101 (Zolgensma) (Cohort 2 only; n=12)	ENDEAR & CS3A (n=100)	CHERISH & CS1,2,10 &12 (n=140)	NURTURE (N=20)	ENDEAR & CHERISH (n=83)
Summary of AEs					
AEs Leading to Discontinuation	0 (0)	16 (16)	0 (0)	0 (0)	16 (19)
Treatment-Related AEs	3 (25)	0 (0)	1 (<1)	0 (0)	0 (0)
Patient Death	0 (0)	17 (17)	0 (0)	0(0)	16 (19)
Incidence of AEs	12 (100)	77 (77)	19 (14)	6 (30)	50 (60)
Common AEs, No. of Events, No. of Patients	NR	1,627 97 (97)	1,187 134 (96)	141 16 (80)	909 82 (99)
Common AEs*					
Pyrexia	6 (50)	59 (59)	49 (35)	5 (25)	39 (47)
URTI	10 (83)	36 (36)	50 (36)	8 (40)	25 (30)
Nasopharyngitis	NR	21 (21)	33 (24)	4 (20)	15 (18)
Vomiting	NR	22 (22)	33 (24)	0 (0)	8 (10)
Headache	NR	0 (0)	51 (36)	0 (0)	0 (0)
Constipation	NR	37 (37)	0 (0)	2 (10)	14 (17)
Back Pain	NR	0 (0)	44 (31)	0 (0)	0 (0)
Cough	NR	15 (15)	26 (19)	3 (15)	17 (20)
Pneumonia	2 (17)	30 (30)	0 (0)	2 (10)	14 (17)
Respiratory Distress	NR	28 (28)	0 (0)	0 (0)	12 (14)
Scoliosis	NR	11 (11)	18 (13)	0 (0)	0 (0)
Diarrhea	NR	16 (16)	0 (0)	0 (0)	7 (8)
Respiratory Failure	3 (25)	26 (26)	0 (0)	0 (0)	16 (19)
Atelectasis	4 (33)	NR	NR	NR	NR
Post-Lumbar Puncture Syndrome	NR	0 (0)	26 (19)	0 (0)	0 (0)

All data are n (%).

AE: adverse event, SAE: serious adverse events, URI: upper respiratory tract infection

*Reported by >10% of participants.

In CL-101, two infants had elevated serum aminotransferase levels after Zolgensma infusion; both were considered treatment related and met criteria for grade 4 AEs (patient 1, cohort 1: 31 times upper limit of normal [ULN] for alanine aminotransferase [ALT] and 14 times ULN for aspartate aminotransferase [AST]; patient 2, cohort 2: 35 times ULN ALT and 37 times ULN AST).²² A protocol amendment requiring oral prednisolone treatment (1 mg/kg) for 30 days starting 24 hours prior to

Zolgensma infusion was added following the first infant's dosing and subsequent serum aminotransferase elevation. Two infants also experienced asymptomatic elevations in serum aminotransferase levels which were deemed nonserious, treatment-related AEs.

3.4 Controversies and Uncertainties

The currently available trials of Spinraza (SMA Types I-III) and Zolgensma (SMA Type I) show prolonged survival and improved motor function compared with historical controls or sham injections. However, there remains considerable uncertainty in the generalizability of the results and in the long-term durability and tolerability of treatment. In particular, for both interventions, the narrow eligibility criteria of trials and the limited sample size (especially for Zolgensma) raises concerns about generalizability of results to the wider population of patients with SMA. The ineligible or otherwise unselected patients are likely more severely ill, experience different or additional comorbidities (e.g., scoliosis), or have a different genetic profile than those selected for the clinical trials. For example, the EAP studies enrolled more heterogeneous patients than in the clinical trials for Spinraza, and treatment with Spinraza had a smaller magnitude of benefit in terms of motor functioning compared with the benefits observed in the clinical trials.

In addition, there is a lack of data on the long-term safety and efficacy of both interventions. The currently-available data do not indicate diminishing benefit, which is promising. Nevertheless, because SMA is a rare disease and the trials have short-term follow-up, understanding the long-term effects of Spinraza or Zolgensma will take time.

For the evidence on Zolgensma, an additional concern is the single-arm design which presents challenges in identifying an appropriate comparison group or “counterfactual.” In other words, we do not know how the 15 patients would have progressed if they had not been treated with Zolgensma. Comparisons with historical controls can exaggerate perceived treatment effects, particularly when standards of care improve over time or when there is a variable natural history,³⁹ which are both true of SMA. For example, in older natural history studies, approximately 68% of patients with Type I SMA died by two years of age. In part due to the improvements in and increased utilization of nutritional and respiratory support, more recent estimates of mortality are approximately 30% at two years of age with approximately half of survivors reliant on noninvasive ventilation. In the trial of Zolgensma, although all 12 patients in the high-dose cohort remained alive and not using permanent ventilation at two years, the outcomes that would have been observed had a concurrent control group been included are unknowable.

Another uncertainty pertinent to Zolgensma relates to the unknown duration of expression of the gene therapy. Gene therapy may provide life-long benefit to patients. On the other hand, if the expression wanes over time, the subsequent treatment pathway is unclear. If antibodies to AAV form, the patient would be unable to receive another dose of Zolgensma. Some patients who received Zolgensma in START went on to take Spinraza after the trial, but the effects of combination

or sequential therapies have not been well studied. In terms of safety, liver toxicity was mitigated by amending the protocol to include an administration of prednisolone before and after Zolgensma infusion. It will be important to monitor liver functioning in patients treated with Zolgensma. Finally, Zolgensma has currently been studied in 15 patients with symptomatic Type I SMA. Early, presymptomatic treatment may provide more benefits to patients, but no data from presymptomatic patients are currently available. Single-arms trials of patients with presymptomatic SMA and other trials with symptomatic SMA Types II-III (other route of administration) are forthcoming (see Appendix C).

For the evidence on Spinraza, an additional source of uncertainty relates to the repeated lumbar punctures in patients, particularly as they age or progress along the disease course. While repeated lumbar punctures were generally tolerated in the clinical trials, some patients required sedation to limit movements during the procedure. The procedure can be further complicated in patients with scoliosis or respiratory complications. In terms of other safety concerns, the Spinraza prescribing information notes the risks of thrombocytopenia and renal toxicity. Finally, although Spinraza has only been studied in patients with SMA Types I-III, it is indicated for patients with SMA of any type. To our knowledge, there are no planned studies to assess the benefits of Spinraza in patients with Type 0 or Type IV. As newborn screening for SMA becomes more common, it is likely that patients will be treated soon, perhaps before developing symptoms. Single-arm trials of patients with presymptomatic SMA are ongoing (see Appendix C).

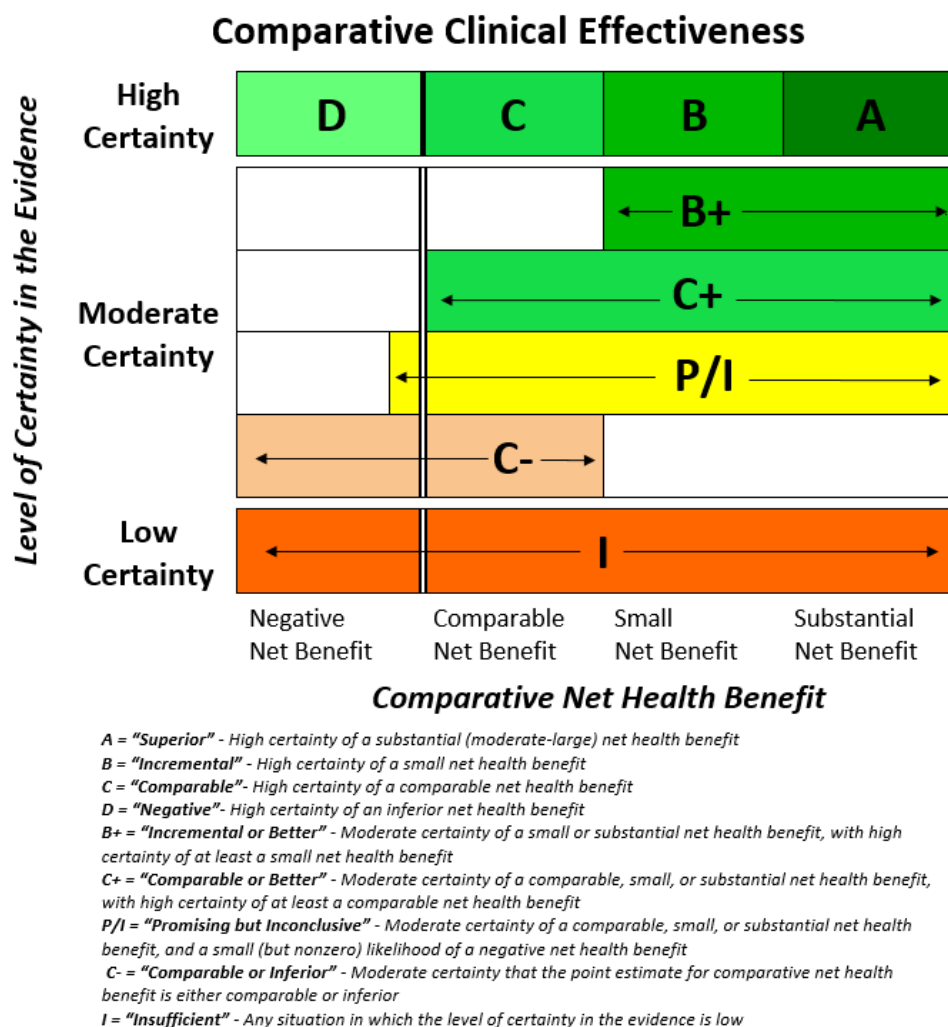
Although it can be tempting to compare the effectiveness of Spinraza and Zolgensma by looking at the results from the ENDEAR and START trials, such comparisons should be avoided. The enrolled populations differed between the trials. For example, there are differences in age at treatment initiation and duration of disease, which are known to be modifiers of treatment effect. In addition, the time point of analysis (median of approximately nine months in ENDEAR and 24 months in START) and approach for assessing motor milestones (HINE-2 vs. WHO) differs between the studies.

3.5 Summary and Comment

SMA is a rare, genetic neuromuscular disease that causes irreversible motor neuron damage that prevents patients from gaining or retaining motor functions. Survival depends on respiratory function, and many infants and children become permanently ventilated. Considering that SMA is a rare disease, the existing evidence base contains many of the common limitations pervasive in rare disease areas, including a small patient population, clinical trial design challenges, and lack of long-term safety and efficacy data. The current limitations of the clinical evidence for Spinraza and Zolgensma include study populations that limit the generalizability of clinical outcomes to SMA patients who differ from those included in the trials, limited long-term safety (e.g., repeated lumbar puncture procedures) and efficacy data (e.g., durability of novel gene therapy), and the uncontrolled, open-label design of the CL-101 trial of Zolgensma. Should additional data regarding

treatment safety and efficacy become available, the conclusions of this report may require updating.

Figure 3.2. ICER Evidence Rating Matrix



We identified several gaps in evidence relevant to our review. Based on the lack of relevant data, we've rated the following evidence in the following populations as "insufficient" (I).

- Type 0 SMA
 - Spinraza
 - Zolgensma
- Later-onset (Types II and III) SMA
 - Zolgensma
- Type IV SMA
 - Spinraza
 - Zolgensma

- Presymptomatic
 - Zolgensma

A comprehensive summary of evidence ratings for Spinraza and Zolgensma for each population defined in Section 1.2 are shown in Table 3.14. Additional details are provided below.

Table 3.14. Evidence Ratings for Spinraza and Zolgensma for SMA

Population	Spinraza	Zolgensma	Ability to Distinguish?
Type 0 SMA	I*	I*	I†
Infantile-Onset (Type I) SMA	A	A	I
Later-Onset (Type II and III) SMA	B+	I*	I†
Type IV SMA	I*	I*	I*
Presymptomatic SMA	B+	I*	I†

*No studies (e.g., RCTs, observational, etc.) identified.

†Comparison is based on lack of available evidence for Zolgensma.

Spinraza for Infantile-Onset SMA

Based on the evidence, Spinraza demonstrated statistically-significant reductions in the need for ventilatory support and improvements in survival. Spinraza was also superior to standard care in improving motor function and milestone achievement, as measured by the HINE-2 and CHOP-INTEND assessments.

We noted some differences between the Spinraza and sham control groups at baseline which suggests more severe symptoms in the Spinraza group. We also noted potentially limited generalizability, as Type I SMA patients with more severe disease were underrepresented in the trials and may not adequately reflect the “real-world” patient population.

Despite these limitations, we have high certainty that Spinraza provides a substantial net health benefit compared to standard care and rate the evidence as “superior” to standard care (A).

Zolgensma for Infantile-Onset SMA

All infants in the Phase I CL-101 trial were alive following at least 24 months of follow-up. Infants also showed gains in CHOP-INTEND motor milestones and most infants who received the proposed therapeutic dose (cohort two) achieved full head control and rolling over motor milestones. Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as “superior” to standard care (A).

Zolgensma versus Spinraza for Infantile-Onset SMA

Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of Zolgensma versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I).

Spinraza for Later-Onset SMA

Based on the single randomized controlled trial of Spinraza in later-onset SMA patients (CHERISH), Spinraza demonstrated statistically-superior improvements in changes from baseline HFMSE, and in the proportion of HFMSE responders, versus the sham control.

Spinraza's superiority in improving HFMSE was evident at the interim analysis, and the study was subsequently terminated early. The interim analysis imputed data from approximately 57% of the enrolled population that had not yet been observed for the full 15-month period. Nevertheless, the final analysis, with 79% (100/126) of patients having been observed for 15-months, continued to show superior benefits of Spinraza on HFMSE scores. Among the 100 patients with observed 15-month data, Spinraza was not superior, however, in improving WHO motor milestone achievements such as unassisted sitting, standing, or walking compared to the sham control.

Similar to ENDEAR, we noted potentially limited generalizability, in that the trial population may not reflect the all patients eligible for treatment. Another limitation is that survival, ventilation, and event-free survival were not evaluated in CHERISH. Finally, we did not find any data regarding long-term safety and durability of clinical benefit.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Spinraza for Presymptomatic SMA

Evidence from the NURTURE trial shows all 25 infants enrolled were alive and four (16%) children met the primary outcome of required respiratory intervention, all of whom had two *SMN2* copies. CHOP-INTEND scores for children with two and three copies were similar and reflected near-maximal motor function. Many children with one year of follow-up, however, had developed one or more clinical symptoms of SMA; the severity of these symptoms are not reported. Furthermore, we found only grey literature (i.e., conference presentations), which have not been peer-reviewed.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Comparison of Evidence Ratings for Spinraza and Zolgensma

The evidence base for Spinraza includes multiple randomized placebo-controlled trials, while the evidence base for Zolgensma is primarily an uncontrolled study in 12 patients. Despite the clear differences in evidence bases, in the ICER rating system, we have rated both therapies as “superior” to standard care (A) for patients with infantile-onset SMA. This judgment reflects that while we have far greater uncertainties about the exact net benefits of Zolgensma than Spinraza, the magnitude of effect in these 12 patients was large enough to have high certainty that Zolgensma provides a substantial net health benefit compared with standard care. Additionally, for both therapies, even if efficacy were maintained only for the duration already observed in the studies evaluating them, we would still assign an “A” rating to the therapies. As stated in [ICER Evidence Rating Matrix: A User’s Guide](#), “We find it useful to consider that conceptual confidence intervals around a point estimate that do not extend beyond a single box of comparative net health benefit represent a ‘high’ level of certainty.” The ratings of “A” for both therapies should not be interpreted to mean that we are able to state that they have similar net benefits, or that we believe the studies within the evidence bases to be of equal quality. It should also not be interpreted to mean that we have similar “conceptual confidence intervals” around net benefits – we do not. Such conceptual confidence intervals are much wider around the net benefit of Zolgensma than Spinraza. However, in each case we judge that the conceptual confidence intervals do not extend below “substantial” net benefit compared with standard care.

4. Long-Term Cost Effectiveness

4.1 Overview

The aim of this economic evaluation was to estimate the cost-effectiveness of Spinraza and Zolgensma, each compared to best supportive care (BSC), from the US health care sector for patients with SMA, in alignment with ICER's [Value Assessment Framework for Ultra Rare Diseases](#). We developed three *de novo* models in Microsoft Office Excel 2016 (Redmond, WA): a model for symptomatic patients with infantile-onset (Type I) SMA; a model for symptomatic patients with later-onset (Type II/III) SMA; and a model for presymptomatic SMA patients. For each population, we estimated the half-cycle corrected lifetime costs, life years gained, and quality adjusted life years (QALYs) gained, discounted at 3% per annum, for Spinraza and BSC. We used these results to generate incremental cost per QALY gained and incremental cost per life-year gained, comparing Spinraza to BSC. We also estimated these outcomes for Zolgensma among patients with Type I SMA and compared the results of Zolgensma versus BSC. Several scenario analyses evaluated the impact of taking a modified societal perspective, alternative survival, cost, and utility assumptions. Although we present a scenario analysis that compares Zolgensma to Spinraza, we did not consider this to be a suitable base case. The rationale for this decision is discussed in Section 4.4. The structure of the models, assumptions, data, and results are described in detail below.

4.2 Methods

Model Structure

The models were dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were explored. The models did not include scoliosis surgery. Figures 4.1 and 4.2 depict the analytic frameworks for the models. Note that the same model structure was used for patients with infantile-onset (Type I) SMA and presymptomatic SMA patients.

The models contained two parts: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model. A brief description of each is provided here, with detailed explanations on assumptions and data presented in subsequent sections.

Figure 4.1. Model Schematic for Patients with Infantile-Onset (Type I) SMA and Presymptomatic SMA Patients

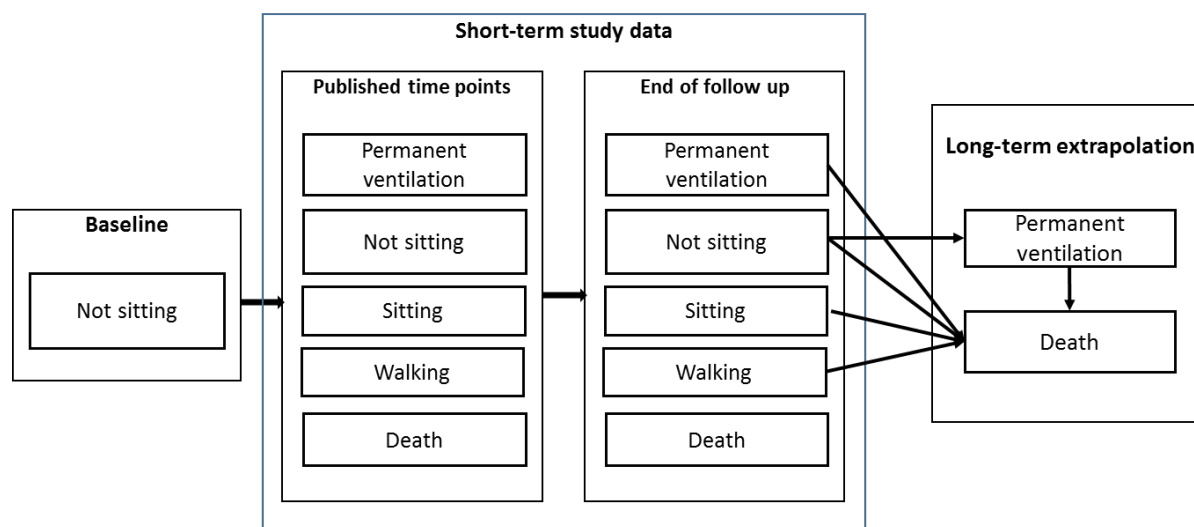
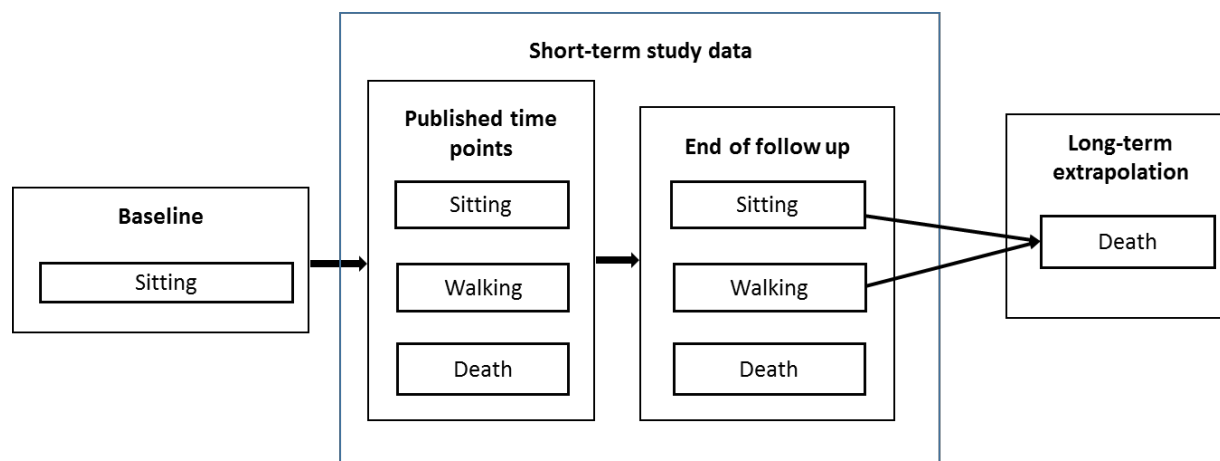


Figure 4.2. Model Schematic for Patients with Later-Onset (Type II/III) SMA



Short-Term Model

Data inputs for each intervention (Spinraza, Zolgensma) were derived from their respective clinical trials and used directly in the model to capture the proportion of the patients in the different health states at different points in time. These data allowed an estimate of the discounted costs, discounted LYs, and discounted QALYs for each of the two interventions and BSC within the study periods. There is no trial of Zolgensma versus BSC, so data from the BSC arm in ENDEAR was used to inform this comparison.

Long-Term Model

The long-term model involved the extrapolation of motor function milestones, permanent ventilation, and mortality, the latter of which was assumed to be conditional on health states. The long-term model used monthly time cycles (i.e., of 30.44 days [365.25 days/12 months]) to estimate lifetime costs and QALYs.

We modeled the extrapolation of motor function milestones over a lifetime using different scenarios. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death). In addition, we also modeled conservative scenarios (only for Type I SMA patients) for the interventions where a proportion of patients lost milestones.

Transition to the permanent ventilation health state in the model was only possible for patients who did not have any motor function milestones (i.e., those in the “not sitting” health state). For these patients, both overall survival (OS) and ventilation-free survival (VFS) were modelled. Patients who achieved motor function milestones were not considered to be at risk of transitioning to permanent ventilation.

Target Populations

The average age and gender distribution at treatment of the SMA populations considered for the model are presented in Table 4.1, which are based on average values reported in the key clinical trials.^{17,20-22}

Table 4.1. Base-Case Model Cohort Characteristics

	Infantile-Onset (Type I) SMA	Later Onset (Type II/III) SMA	Presymptomatic SMA
Mean Age	4.4 months	2 years	21 days
Female	55%	50%	52%

Treatment Strategies

The interventions of interest were Spinraza and Zolgensma. Spinraza is administered per its labelled indication as four initial loading doses and once every four months thereafter using intrathecal injection. Zolgensma is a one-time therapy administered using single intravenous infusion. The interventions were compared to BSC, consisting of standard respiratory, gastrointestinal, and nutritional care for SMA patients.

Key Model Choices and Assumptions

The assumptions for the base-case model are described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
The analyses used a naïve comparison between Zolgensma and BSC, and Spinraza and BSC.	There are no head-to-head trials comparing Zolgensma to the other interventions, and individual patient data (IPD) would be needed to perform matched, adjusted indirect comparisons or simulated treatment comparisons. As IPD were not available, only a naïve comparison is possible. Thus, the model compared the results of Zolgensma to BSC and Spinraza to BSC without any adjustment for differences in patient characteristics between the studies.
Data from the trials and studies on motor function milestones, permanent ventilation, and mortality were used directly in the short-term model.	Robust estimation of disease progression parameters (e.g., transition probabilities) was not possible without access to IPD from the trials and studies. As such, data for the different interventions during the study period were used directly in the model to estimate short-term costs/QALYs.
In the short-term model for Spinraza, we assumed that the proportion of patients sitting among those alive who are not followed up is the same as the observed proportion of patients sitting among who attended the follow up visits.	The proportion of patients reported sitting in Castro et al. ²⁰ are based on those attending the follow-up visits at that time point and we do not know the proportion of patients who were able to sit among those who did not attend follow up visits. As such, we assumed that they are the same.
Motor function milestones achieved at the end of the follow up are sustained until death.	There were no long-term data on the extrapolation of motor function milestones identified; the base-case analyses assume that these milestones are sustained until death. However, alternative scenario analyses were also considered.
Utility benefit was assumed in the treatment arms for patients achieving interim motor function milestones such as head control, rolling, crawling, and standing.	Although interim milestones are not modelled as explicit health states in the model, utility benefit was assumed in the treatment arms to account for achieving these interim milestones. This was implemented as additional utility benefit in treatment arms for the “not sitting” and “sitting” health states.
Only patients in the “not sitting” health state can transition to “permanent ventilation” state.	Clinical experts deemed it reasonable to assume that patients achieving motor function milestones are not at risk of permanent ventilation.
In the BSC arm, for patients in the “not sitting” health state at the end of the short-term model, a partitioned survival modelling approach was used to estimate the proportions of patients dying and moving to permanent ventilation.	The data sources only reported the OS and the VFS, so the VFS curve is subtracted from the OS curve to estimate the proportion of patients in “permanent ventilation” health state.
In the treatment arms, we assumed that patients in the “not sitting” health state at the end of the short-term model had the same survival as those on “permanent ventilation”.	The data show better survival in “permanent ventilation” state than “not sitting” state. As such, we made this assumption to account for the survival benefit in the treatment arms for achieving interim milestones such as head control and rolling among patients in the “not sitting” health state. This is an assumption favorable to the drug given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit.

No explicit transitions from “not sitting” to “permanent ventilation” were modelled in the treatment arms.	We did not know the transition between these two health states. However, additional costs for permanent ventilation were included for three months prior to death in the “not sitting” state
Patients with SMA Type I who are in “sitting” health state are assumed to have mortality similar to that of SMA Type II patients.	Clinical experts deemed it reasonable to assume that SMA Type I patients who can sit have similar prognosis as SMA Type II patients who are able to sit but not walk.
Patients with SMA Type I who are in “walking” health state are assumed to have mortality similar to that of SMA Type III patients.	Clinical experts deemed it reasonable to assume that SMA Type I patients who can walk have similar prognosis to SMA Type III patients who are able to walk.
Patients on Spinraza who did not achieve motor function milestones at 24 months discontinued the treatment. We assumed no other patients discontinue Spinraza in the model.	In the Spinraza model submitted to the National Institute for Health and Care Excellence (NICE), this was assumed to be 13 months. However, our model used 24 months to reflect the patients who continue to receive Spinraza, as observed in SHINE ²⁰ extension study.
AE costs and disutilities were not included in the model.	Given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
The costs of BSC are not broken out beyond the health state costs in the model.	It is likely that the health state costs included in the model already include the costs of BSC.
The transition probabilities were not adjusted for age at the start of treatment in the SMA Type I model.	The data sources used to estimate the mortality risks for SMA Type I patients have similar starting ages, so they are not explicitly adjusted for age at treatment.
None of the patients in the Zolgensma arm are assumed to die in the short-term model.	None of the 12 patients receiving Zolgensma in the single arm study ²² had died at the last follow up and as such this is reflected in the short-term model. Given the small sample size, we acknowledge that it may be misrepresentative of real-world scenarios to assume that no patients on Zolgensma will ever die in the short-term model.

Model Inputs

In the subsections below, we first present the health state inputs for each of the short-term models (i.e., infantile-onset SMA, later-onset SMA, and presymptomatic SMA). The health state inputs for long-term extrapolation are common across these models, and as such are presented together in the next subsection. In subsequent sections, health state utilities, costs, and productivity gains are presented.

Infantile-Onset (Type I) SMA Short-Term Model

Motor Function Milestones

The data on proportions of Spinraza patients achieving motor function milestones at different time points for the different interventions were based on the ENDEAR trial¹⁷ and SHINE study.²⁰ For Spinraza, Castro et al.²⁰ reported the proportion of patients achieving sitting at different time points, which are presented in Table 4.3.

Table 4.3. Motor Function Milestones Achieved on Spinraza

	Baseline n=81	Day 64 n=70	Day 183 n=65	Day 302 n=51	Day 394 n=48	Day 578 n=31	Day 698 n=17
% Achieving Independent Sitting (But Not Walking)	0	1	5	10	15	29	24
% Achieving Walking	0	0	0	0	0	0	0

With different numbers of patients at risk at these time points, we followed a multi-stage process to estimate the true proportions of Spinraza patients achieving the milestones (i.e., proportions using n=81 at the baseline) as described in Appendix Table E2.

No patients in the BSC arm were assumed to achieve any motor function milestones at any time points since the trial reported that 0% of the patients in the sham control group achieved the ability to sit independently during assessments at days 183, 302, or 394. We could not include longer-term data on this estimate in the BSC arm as all sham control patients in ENDEAR¹⁷ switched to Spinraza treatment in SHINE, an OLE trial.²⁰

For Zolgensma, we used the data submitted in confidence by the manufacturer. This academic-in-confidence data will be unmasked no later than November 2020 per [ICER's Data-in-Confidence policy](#). Five of 12 patients treated with Zolgensma were started on Spinraza at the end of the study period; however, two of these patients discontinued, leaving three patients on treatment. As it was not clear whether these patients were not sitting, sitting, or walking, we assumed that they were in the sitting health state, which had the greatest proportion (75%) of patients at the end of the short-term model. So, a third of the patients in the "sitting" health state at the end of the short-term

model (i.e., three out of nine) in the Zolgensma arm received Spinraza. As we did not know whether they received Spinraza because their health state started to deteriorate or because they did not improve as much as desired, we assumed that half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth ($33\% * 50\%$) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period.

Mortality

The proportions of patients alive at different time points were estimated from the OS data presented for each intervention. The OS data for Spinraza were from patients who received Spinraza in both ENDEAR¹⁷ and SHINE.²⁰ The OS data for BSC were from patients who received sham control in ENDEAR, but only the data until the end of the ENDEAR trial period were used in the model, as all sham control patients switched to Spinraza in SHINE.²⁰

None of the 12 patients receiving Zolgensma in the single-arm study²² died at the last follow-up of 24 months, and this is reflected in the model. Given the small sample size, we acknowledge this may not be representative of real-world scenarios to assume 100% survival in the short-term model.

Permanent Ventilation

The VFS rates at different time points were estimated from the combined VFS data in ENDEAR¹⁷ and SHINE,²⁰ and subtracted from the OS data to estimate the proportion of patients under permanent ventilation for the Spinraza arm. The VFS data for BSC were from patients who received sham control in ENDEAR¹⁷ alone. We did not use data from SHINE²⁰ since patients in the sham control arm in ENDEAR¹⁷ were switched to Spinraza in SHINE. None of the 12 patients receiving Zolgensma in the single-arm study²² received permanent ventilation at the last follow up, and this is reflected in the model.

Not Sitting

In the short-term model, the proportion of patients in the “not sitting” health state was estimated as the complement of the sum of proportions of patients on permanent ventilation, patients achieving milestones, and patients that died. That is, patients not in any of the above health states remained in the “not sitting” health state.

When estimating these proportions, patients were assigned to the highest milestone. That is, if a patient achieved both sitting and walking, they were accounted for in the “walking” health state but not accounted for in the “sitting” health state.

Later-Onset (Type II/III) SMA Short-Term Model

Motor Function Milestones

The short-term model for patients with later onset SMA assumed that the Spinraza patients remain in the “sitting” health state until the end of the short-term model based on trial data,¹⁸ where none of the patients achieved the ability to walk independently and only one patient (out of 84) was able to walk with assistance.

Trial results showed that none of the patients in the sham control arm (n=42) achieved the ability to walk independently or walk with assistance.¹⁸ As such, the model assumed that the BSC patients remain in the “sitting” health state until the end of the short-term model.

Presymptomatic SMA Short-Term Model

Effectiveness of Spinraza in achieving motor function milestones in presymptomatic patients was estimated from the NURTURE study.²¹ The model for symptomatic SMA Type I patients was adapted to estimate the costs and QALYs for presymptomatic SMA patients. As the NURTURE study²¹ does not report which patients would have been SMA Type I or SMA Type II/III, the proportions of these patients were estimated based on *SMN2* copies and expected proportions of different SMA types in the real world. The proportions of patients with SMA Type I, SMA Type II and SMA Type III in the presymptomatic model were 60%, 30%, and 10% respectively. These proportions were derived by assuming that the patients with two *SMN2* copies (n=15) were SMA Type I patients and the patients with three *SMN2* (n=10) copies were SMA Type II and SMA Type III patients.

Exploratory analyses were also performed to estimate the cost-effectiveness of a hypothetical drug which has the costs of Zolgensma and efficacy of Spinraza in the presymptomatic SMA population.

Long-Term Model

Extrapolation of Motor Function Milestones

Motor function milestones in the long-term model were extrapolated based on milestone status at the end of the short-term model, with a base-case assumption that milestone status remained the same until death.

As stated earlier in this section, we also modeled more conservative scenarios (for SMA Type I patients only), where we assumed that a proportion (ranging from 10% to 30%) of patients in the “sitting” health state lost their motor function milestones.

Extrapolation of Mortality and Permanent Ventilation

At the end of the short-term model, patients were in one of the following health states: “permanent ventilation,” “not sitting,” “sitting,” or “walking.” Those in the “not sitting” health state in the BSC arm could either transition to permanent ventilation or die, and we modeled both, both OS and VFS for these patients. For those in the treatment arms, we modeled transition to only death and not permanent ventilation among those in the “not sitting” health state. However, we included the costs for permanent ventilation for the three months prior to death for those transitioning to death from this health state. The patients in all other health states were not considered to be at risk of transitioning to permanent ventilation and, as such, could only transition to death.

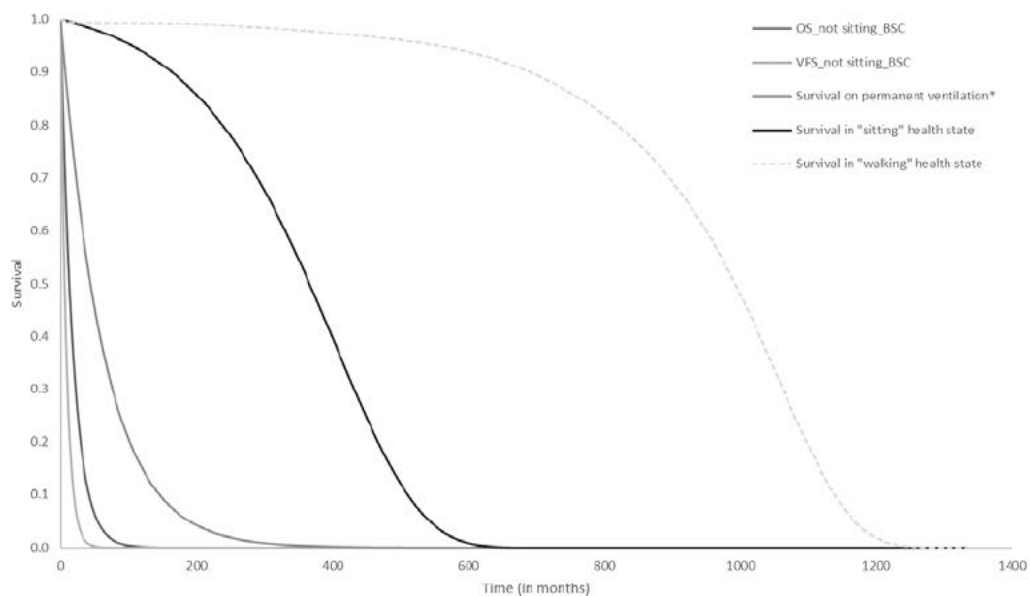
The long-term risks of mortality associated with each of the health states were modelled by fitting survival curves to digitized, published Kaplan-Meier (KM) data most relevant to each health state. We digitized the KM data and reconstructed the individual data using the methods described in Guyot et al.⁸⁰ We fitted different parametric distributions (exponential, Weibull, gamma, Gompertz, log-normal, log-logistic, and generalized gamma) to this survival data. We identified the best fitting curves based on a combination of clinical plausibility, fit statistics such as Akaike information criteria (AIC) and Bayesian information criteria (BIC), and visual inspection. For each health state, a single parametric distribution was selected to calculate the estimated probability of death in each time period (e.g., a given month).

The transitions from different health states, assumptions, data sources, and parametric distributions selected to extrapolate survival are presented in Table 4.4. The survival curves used in the base-case analysis for long-term extrapolation are presented in Figure 4.3. Appendix Tables E3-E6 presents the data on AIC and BIC, along with plots of the different parametric distributions.

Table 4.4. Summary of the Long-Term Extrapolation

	Description	Assumption	Source	Distribution Selected	Parameters
Not Sitting (BSC Arm)	OS	Assumed to be same as BSC patients	ENDEAR sham control arm ¹⁷	Exponential	$\lambda_{tw}=0.0127$
	VFS	Assumed to be same as BSC patients	ENDEAR sham control arm ¹⁷	Exponential	$\lambda_{tw}=0.0276$
Not Sitting (Treatment Arms)	OS	Assumed to be same as when on permanent ventilation	Gregoretti et al ⁴⁰ (NRA curve)	Exponential	$\lambda_{tm}=0.0158$
	VFS	Not explicitly modelled	--	--	--
Permanent Ventilation	Mortality	Assumed to be same as patients on non-invasive respiratory muscle aid, including non-invasive ventilation, tracheostomy, or mechanically assisted cough	Gregoretti et al ⁴⁰ (NRA curve)	Exponential	$\lambda_{tm}=0.0158$
Sitting	Mortality	Assumed to be same as SMA Type II patients	Zerres and Schöneborn et al. ⁴¹	Gompertz	$\alpha=0.0964$, $\beta=0.0037$
Walking	Mortality	Assumed to be same as general population	US population mortality ⁸¹	--	--

Figure 4.3. Survival Curves Used in the Long-Term Extrapolation Model



BSC: best supportive care, OS: overall survival, VFS: ventilation-free survival

*Survival in “not sitting” health state in treatment arm is the same as survival on permanent ventilation.

In Figure 4.3, the OS and VFS curves represent the overall survival and ventilation-free survival of the patients in the “not sitting” health state in the BSC arm, which were assumed to be the same as

that of the patients in the sham control arm of ENDEAR. The OS curve represents the survival of patients in the “not sitting” health state at the end of the short-term model, with a mean survival time of 1.55 years. The VFS curve, with a mean survival of 0.74, is subtracted from the OS curve to estimate the patients in the permanent ventilation health state that moved from the “not sitting” health state in the long-term model.

The curve “survival on permanent ventilation” represents the survival of patients in the “permanent ventilation” health state at the end of the short-term model, with a mean survival of 5.3 years. The survival in the “not sitting” health state in the treatment arms is assumed to be the same as the survival on “permanent ventilation.”

The “sitting” curve represents the survival of patients in the “sitting” health state at the end of the short-term model, based on the assumption that they have the same survival as SMA Type II patients, with a mean survival of 29.3 years. The “walking” curve represents the survival of patients in the “walking” health state at the end of the short-term model, based on the assumption that they have the same survival as the general population, with a mean survival of 78.7 years.

Permanent Ventilation and Mortality from the “Not Sitting” Health State in the BSC arm

Patients in the “not sitting” health state in the BSC arm can transition to either the “permanent ventilation” health state or to death. We used the BSC arm of the ENDEAR study; the OS and VFS curves were digitized from the KM data presented in the study. At each monthly cycle, the proportions of patients dying from this health state were estimated from the OS curve, and the VFS curve was subtracted from the OS curve to estimate the proportion of patients in the “permanent ventilation” health state.

Permanent Ventilation and Mortality from the “Not Sitting” Health State in the treatment arms

The patients in the “not sitting” health state in the treatment arms were assumed to have the same mortality as in the “permanent ventilation” health state. This is to account for the survival benefit of the “not sitting” patients in the treatment arms for achieving interim milestones such as head control and rolling. No explicit transitions from “not sitting” to “permanent ventilation” were modelled, however, additional costs for permanent ventilation were included for three months prior to death in the “not sitting” state.

Mortality from the “Permanent Ventilation” Health State

We used retrospective data⁴⁰ of SMA Type I patients from four Italian centers from 1992 to 2010 to model mortality in the “permanent ventilation” health state. In this study, 31 patients required continuous non-invasive respiratory muscle aid, including non-invasive ventilation and mechanically assisted cough (n=31). Of these 31 patients, seven also received tracheostomy.

Mortality from the “Sitting” Health State

Treated SMA Type I patients who can sit were assumed to have similar prognosis as SMA Type II patients who are able to sit but not walk. Pooled data from German and Polish studies on SMA Type II patients (n=240) presented in Zerres and Schöneborn et al.⁴¹ were used to model mortality from the “sitting” health state.

Mortality from the “Walking” Health State

Treated patients with Type I SMA who can walk are assumed to have similar prognosis as patients with SMA Type III who are able to walk. A previously-conducted study⁴¹ reported no significant reduction in lifespan among SMA Type III patients compared to the general population. As such, we use the general population mortality⁸¹ for patients with Type I SMA who can walk.

Health State Utilities

Patient Utilities

The utilities used in the base-case analyses were derived from multiple sources and are presented in Table 4.5. The utilities reported by Thomson et al. in 2017⁴² were from a cross-sectional study of individuals with SMA in Europe; investigators collected parent/proxy-assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version. The mean utility value for patients with Type I SMA in the UK was 0.19 (n=7); we assumed this value was the same for both “permanent ventilation” and “not sitting” health states.

The utility for the “sitting” health state was sourced as 0.6 from the Tappenden et al.⁴³ evidence review group (ERG) report evaluating the submission of Spinraza for NICE. Tappenden et al. report the utilities elicited from the clinical experts who advised the ERG, who were asked to provide plausible utility estimates for the different health states; it should be noted that these utility estimates are not preference-based.

We assumed additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. The proportions of patients achieving these interim milestones were not available at different time points, so the model assumed an additional utility benefit for all patients in the “not sitting” and “sitting” health states. This was implemented in the model as a utility of 0.29 for the “not sitting” health state (i.e., an additional utility of 0.1 compared to BSC) and a utility of 0.65 for the “sitting” health state (i.e., an additional utility of 0.05 compared to BSC).

The utility for the “walking” health state was sourced from general population utilities⁴⁴, as presented in Table 4.6. A scenario analysis was also performed using a utility value of 0.878 for

patients in the “walking” health state, based on a study by Thomson et al.⁴² which provided parent-proxy assessment of quality of life.

All utilities were capped at the general population utility for that age group, to ensure they did not exceed the utilities of the general population. Also, we used the utility for 18-29 age group presented in Table 4.6 as the utility for patients in the “walking” health state aged less than 18.

Table 4.5. Patient Utility Values for Health States

	Utility Value (BSC Arm)	Source	Utility Value (Treatment Arms)	Source
Permanent Ventilation	0.19	Thomson et al., 2017 ⁴²	0.19	Thomson et al., 2017 ⁴²
Not Sitting	0.19		0.29	Assumption
Sitting	0.60	Tappenden et al., 2018 ⁴³	0.65	Assumption
Walking	--	General population utility ⁴⁴	--	General population utility ⁴⁴

Table 4.6. General Population Utility Values

Age Group	Mean	Std. Error
18-29	0.922	0.0019
30-39	0.901	0.0021
40-49	0.871	0.0024
50-59	0.842	0.0028
60-69	0.823	0.0034
70-79	0.790	0.0036
>=80	0.736	0.0062

Cost Inputs

The costs used in the model include treatment costs, administration/monitoring costs, and costs associated with being in each health state. All costs were inflated to 2017 values using the methods described in the [ICER Reference Case](#).

Drug Acquisition Costs

The recommended dosage for Spinraza is four loading doses (the first three loading doses administered at 14-day intervals with the fourth loading dose administered 30 days after the third dose) and a maintenance dose administered once every four months thereafter. Since Spinraza is administered in a hospital setting, we included mark-ups associated with the treatment aligning with the [ICER Reference Case](#). We used the average wholesale price (AWP) to which we applied a

15% discount, reflecting the weighted average mark-ups seen for treatments administered specifically in a hospital outpatient setting.⁸²

Zolgensma is potentially a one-time therapy administered using a single intravenous infusion. Zolgensma currently has no publicly-known list or net price; we therefore used a placeholder price for Zolgensma, as forecast by a market analyst estimate.⁸³ These costs are presented in Table 4.7.

Table 4.7. Treatment Cost Inputs

Intervention	Administration	Package Size	WAC* per Package	Estimated Net Cost per Package†	Source
Spinraza	Intrathecal injection	2.4 mg/ml (5 ml)	\$125,000	\$127,500	Redbook 2018 ⁸⁴ ; Magellan 2016 ⁸²
Zolgensma	Intravenous infusion	--	--	\$2,000,000‡	Market analyst estimate ⁸³

*Wholesale acquisition cost (WAC) as of November 2, 2018.

†AWP – 15%, where AWP is \$150,000 per package as of November 2, 2018.

‡Placeholder price.

Administration and Monitoring Costs

All administration, laboratory, and monitoring costs associated with the treatments are presented in Tables 4.8 and 4.9. For Spinraza, it was assumed that 40% of the patients receive the treatment in an inpatient setting and accrue the costs of inpatient stay and anesthesia. For Zolgensma, it was assumed that the infusion will last two hours and that the costs of prednisolone are only for the first month.

Table 4.8. Costs Associated with Spinraza Treatment

	Cost	Description	Source
Intrathecal Injection (Lumbar Puncture into Central Nervous System)	\$82.44	Current Procedural Terminology (CPT) code 96450	Physician fee schedule 2018; ⁸⁵ facility price
Intrathecal Injection (Drain Cerebrospinal Fluid)	\$86.76	CPT 62272	
MD/Specialist	\$52.20	CPT 99213	
Monitor for Thrombocytopenia	\$5.53	CMS laboratory fee schedule 85049	
Monitor for Renal Toxicity	\$10.72	CMS laboratory fee schedule 80069	
Anesthesia for Lumbar Puncture	\$133.13	HCPCS 00635	
Imaging (Ultrasound or Fluoroscopy – Average Cost)	\$78.66	CPT 77003, 76942	
Inpatient Cost per Diem (Routine Surgery)	\$1,316	Using a cost:charge ratio of 1:3	Nationwide Children’s Hospital ⁸⁶
Inpatient Anesthesia	\$583	Using a cost:charge ratio of 1:3	
Total Administration Cost	\$1,209	Assuming 40% of patients receive Spinraza in inpatient settings	

Table 4.9. Costs Associated with Zolgensma Treatment

	Cost	Description	Source
Single Dose Intravenous Infusion	\$74.16 \$22.32 per additional hour	CPT 96365 CPT 96366	Physician fee schedule 2018; ⁸⁵ facility price
Anti-AAV9 Diagnostic Test	\$15.89	CPT 86603	
Laboratory Monitoring	\$10	CPT 80069	
Prednisolone	\$15	Oral, 1 mg/kg 30-day prescription	Redbook 2018 ⁸⁴
Total Administration Cost	\$137	Assuming the infusion is for two hours	

Health Care Utilization Costs

The monthly costs associated with the different health states are presented in Table 4.10. They were sourced from a claims analysis of commercial health plans comprising infantile-onset SMA (n=23), childhood-onset SMA (n=22) and later-onset SMA (n=296) patients, based on the study reported by Shieh et al.⁸⁷ The costs of infantile SMA patients were used for the “not sitting” health state. The costs of childhood-onset SMA and later-onset SMA were used for the “sitting” and “walking” health states, respectively.

The costs in the “permanent ventilation” health state were estimated as the costs associated with permanent ventilation added to the costs of the “not sitting” health state. These included the costs of equipment and disposable equipment and supplies that are associated with ventilator-dependent children living at home, estimated from a UK study by Noyes et al.⁸⁸ These costs were converted into US dollars using 2002 exchange rates⁸⁹ and then inflated to 2017 dollars. The additional costs of permanent ventilation were estimated as \$32,413 per year, which translates to an additional monthly cost of \$2,701. In total, the monthly costs of the permanent ventilation health state were estimated as \$28,218.

Table 4.10. Background Costs in Different Health States

	Permanent Ventilation	Not Sitting	Sitting	Walking
Inpatient Hospitalization	\$21,863	\$21,863	\$3,401	\$1,116
Outpatient Services	\$3,341	\$3,341	\$2,631	\$984
Emergency Services	\$313	\$313	\$325	\$399
Costs Specific to Permanent Ventilation	\$2,701	--	--	--
Total Monthly Cost	\$28,218	\$25,517	\$6,357	\$2,499

Scenario analyses were performed using cost data from Armstrong et al.⁹⁰ who reported additional total annual health care costs for patients with SMA diagnosed before and after one year of age, respectively. Scenario analyses were also performed using cost data from a report by the Lewin Group⁹¹ that reported additional total annual health care costs broken out for patients with early onset and other types of SMA.

Non-Medical Costs

Annual non-medical costs associated with the different health states were obtained from a report by the Lewin Group,⁹¹ and are summarized in Table 4.11. We excluded the “professional caregiving” costs from non-medical costs, as the costs in the “professional caregiving” category included some costs that we considered to medical (e.g., home health aides, skilled nurses, or nurse assistants) and others that may be incurred by health care payers (e.g., government programs, insurance, etc.). While this category also included some types of paid caregiving that would not be considered as medical (e.g., “relatives/friends who are paid by families or state programs to care for the affected persons”), the proportions of medical versus non-medical costs were not reported.

In a scenario analysis using a modified societal perspective, we used a weighted average of early onset and other SMA patients’ non-medical cost for all health states (except the walking health state, which had zero non-medical costs). The costs, which included moving or modifying the home and purchasing or modifying a vehicle, were estimated as mean annual costs but the follow-up period was not clear. Given this, these costs were assumed as recurring costs in the model, rather than stopping or changing over time.

Table 4.11. Monthly Non-Medical Costs

	Permanent Ventilation	Not Sitting	Sitting	Walking
Total Costs	\$964	\$964	\$964	\$0

Patient Productivity Gains

Patient productivity gains are included in a scenario analysis using a modified societal perspective. No productivity changes were assumed for those in the “permanent ventilation” and “not sitting” health states. For other health states, data from the Lewin Group report⁹¹ on educational attainment for SMA patients were combined with data on income by education level in the US from the Bureau of Labor Statistics⁹² to estimate the productivity gains of patients. These proportions were weighted by monthly earnings to estimate the potential monthly income as \$4,450, as shown in Appendix Table E7. These productivity gains are estimated from the age of 25 years until an age of 67 years.

Sensitivity Analyses

One-way sensitivity analyses were performed using plausible ranges based on published data and expert opinion to identify the key drivers of model outcomes. Probabilistic sensitivity analysis (PSA) was performed by jointly varying all model parameters, using 1,000 simulation runs. Due to the lack of data, the distributions used for costs and utilities in the PSA are on mean values $\pm 20\%$. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses.

Additionally, a threshold analysis was performed by calculating the drug prices that would achieve willingness-to-pay (WTP) thresholds between \$50,000 and \$500,000 per QALY.

Scenario Analyses

In addition to the base-case analysis, we conducted the following scenario analyses:

- Analyses using a modified societal perspective
- Analyses excluding health care costs other than those directly related to treatment with Spinraza or Zolgensma for patients with Type I SMA
- Zolgensma compared to Spinraza for patients with Type I SMA
- Analyses using alternative utility estimates
- Analyses using alternative health state costs
- Not accounting for utility benefits of achieving interim milestones (such as head control, rolling, crawling, and standing)
- Exploratory analysis of a hypothetical drug with the costs of Zolgensma and efficacy of Spinraza in presymptomatic patients

- Conservative scenario where the patients lose milestones, and have lower survival and utility in “sitting” and “walking” health states
- Analyses using a 10-year time horizon
- Analyses using 1.5% discounting

Model Validation

Several approaches were undertaken to validate the model. First, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. Second, model input parameters were varied to evaluate the face validity of changes in results. As part of ICER’s initiative for modeling transparency, we shared the model with AveXis for external verification shortly after publishing the draft report for this review. Biogen chose not to receive the model. The outputs from the model were validated against the trial and study data of the interventions as well as any relevant observational datasets. Finally, the results were compared to other cost-effectiveness models in this therapy area.

4.3. Results

For each of the three modeled SMA sub-types, base-case results are presented from the health care sector perspective. Costs and cost-effectiveness ratios are rounded to the nearest \$1,000.

Infantile-Onset (Type I) SMA Model

Base-Case Results

Tables 4.12 and 4.13 present the base-case results from the health care sector perspective. Table 4.12 presents the results for the Spinraza versus BSC comparison, while Table 4.13 presents the results for the Zolgensma versus BSC comparison. The breakdown of LYs, QALYs, and costs according to health state for the different interventions are presented in Appendix Tables E10 to E13.

In the Type I SMA population, the total costs in the Spinraza arm were approximately \$3.9 million, which is just under five times the total costs in the BSC arm of around \$790,000. However, the Spinraza arm has higher QALYs and LYs (3.24 and 7.64, respectively) compared to the BSC arm (0.46 QALYs and 2.40 LYs, respectively). This resulted in an incremental cost per QALY gained of approximately \$1,112,000 and an incremental cost per LY gained of \$590,000 for Spinraza compared to BSC.

Table 4.12. Base-Case Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	3.24	7.64	\$1,112,000	\$590,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

In the Type I SMA population, the total costs in the Zolgensma arm (using a placeholder price of \$2 million) were approximately \$3.7 million, which is just under five times the total costs in the BSC arm of around \$790,000. However, the Zolgensma arm has higher QALYs and LYs (12.23 and 18.17, respectively) compared to the BSC arm (0.46 QALYs and 2.40 LYs, respectively). This resulted in an incremental cost per QALY gained of \$243,000 and an incremental cost per LY gained of \$182,000 for Zolgensma compared to BSC.

Table 4.13. Base-Case Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,657,000	\$3,657,000	12.23	18.17	\$243,000	\$182,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

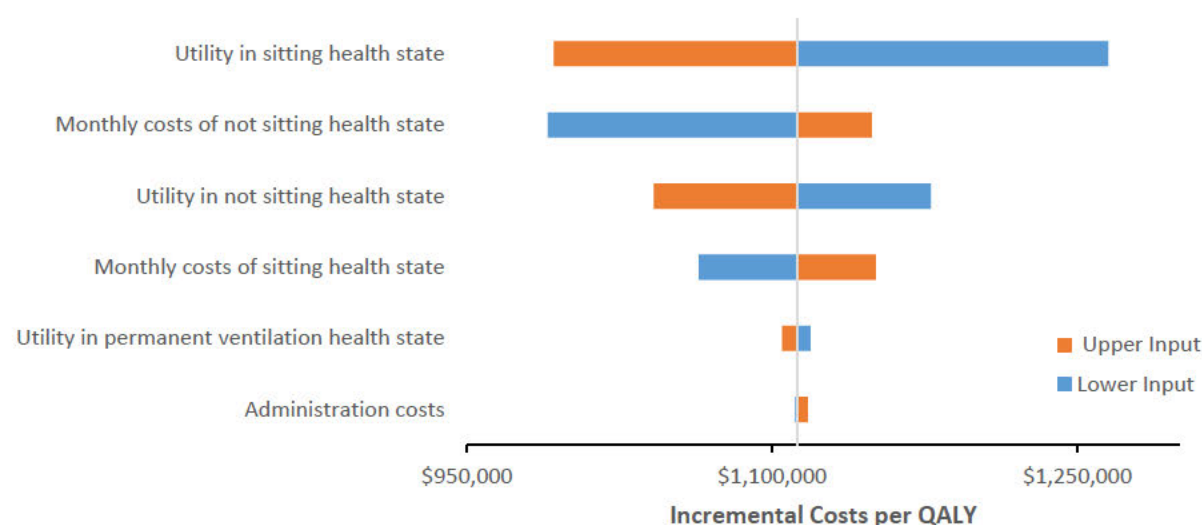
*Placeholder price.

Sensitivity Analyses Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY.

For the Spinraza versus BSC comparison, key drivers of uncertainty included monthly costs and utility values for the “sitting” and “not sitting” health states (Figure 4.4 and Table 4.14). In probabilistic analyses, Spinraza did not achieve a greater than zero likelihood of meeting the \$500,000/QALY or lower threshold across the range of values tested (Table 4.16 and Figures E5 and E6 in Appendix E).

Figure 4.4. Tornado Diagram for One-Way Sensitivity Analyses of Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective



QALY: quality-adjusted life year

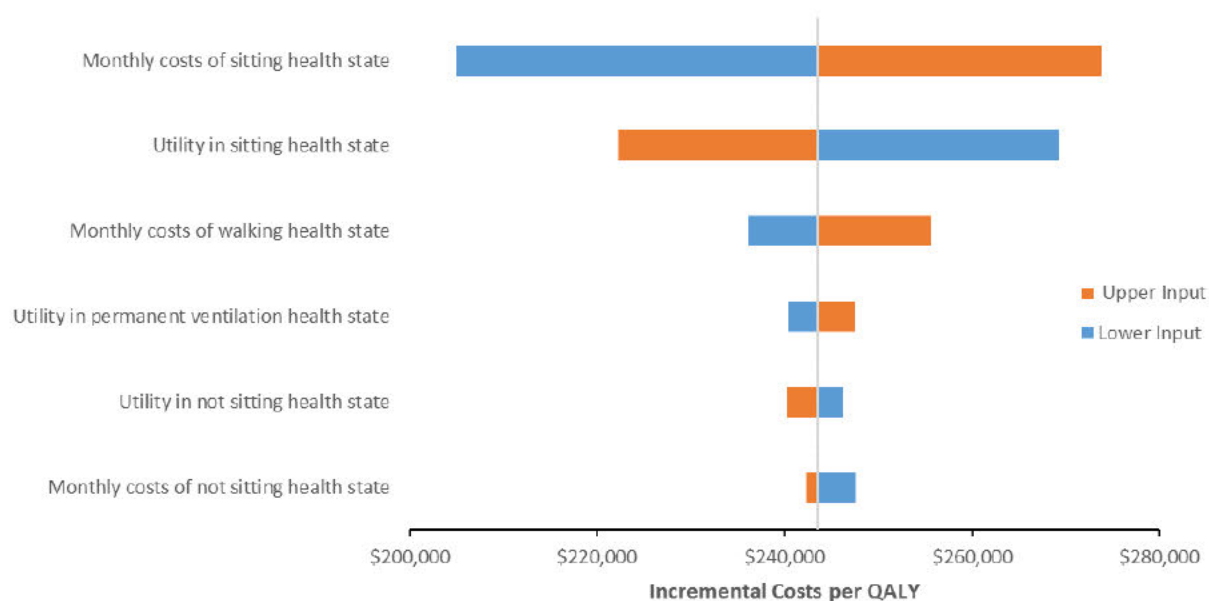
Table 4.14. Tornado Diagram Inputs and Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Utility in Sitting Health State*	\$993,000	\$1,265,000	0.5	0.7
Monthly Costs of Not Sitting Health State	\$990,000	\$1,149,000	\$10,434	\$30,000
Utility in Not Sitting Health State*	\$1,042,000	\$1,178,000	0.1	0.3
Monthly Costs of Sitting Health State	\$1,064,000	\$1,151,000	\$3,000	\$9,000
Utility in Permanent Ventilation Health State*	\$1,105,000	\$1,119,000	0.1	0.3
Administration Costs	\$1,111,000	\$1,117,000	\$1,000	\$2,000

*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

For the comparison of Zolgensma versus BSC, key drivers of uncertainty included monthly costs in the “sitting” and “walking” health states and the utility in the “sitting” health state (Figure 4.5, Table 4.15). In probabilistic sensitivity analyses, Zolgensma achieved a 0.1% chance of meeting the \$150,000/QALY threshold (Table 4.16 and Figures E7 and E8 in Appendix E).

Figure 4.5. Tornado Diagram for One-Way Sensitivity Analyses of Zolgensma* versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective



QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

Table 4.15. Tornado Diagram Inputs and Results for Zolgensma* versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Monthly Costs of Sitting Health State	\$205,000	\$274,000	\$3,000	\$9,000
Utility in Sitting Health State†	\$222,000	\$269,000	0.5	0.7
Monthly Costs of Walking Health State	\$236,000	\$256,000	\$1,000	\$5,000
Monthly Costs of Not Sitting Health State†	\$242,000	\$248,000	\$10,434	\$30,000
Utility in Permanent Ventilation Health State	\$240,000	\$247,000	0.1	0.3
Utility in Not Sitting Health State†	\$240,000	\$246,000	0.1	0.3

*Based on a placeholder price of \$2,000,000.

†Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table 4.16. Probabilistic Sensitivity Analyses Results in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Spinraza vs. BSC	Zolgensma* vs. BSC
Cost-Effective at \$50,000/QALY	0%	0%
Cost-Effective at \$100,000/QALY	0%	0%
Cost-Effective at \$150,000/QALY	0%	0.1%
Cost-Effective at \$200,000/QALY	0%	0.7%
Cost-Effective at \$250,000/QALY	0%	62.5%
Cost-Effective at \$300,000/QALY	0%	100%
Cost-Effective at \$350,000/QALY	0%	100%
Cost-Effective at \$400,000/QALY	0%	100%
Cost-Effective at \$450,000/QALY	0%	100%
Cost-Effective at \$500,000/QALY	0%	100%

BSC: best supportive care, QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

Scenario Analyses Results

We performed a number of scenario analyses to identify the effect of alternative inputs and assumptions on the cost-effectiveness results.

Tables 4.17 and 4.18 present the results from a scenario analysis taking a modified societal perspective, which includes patient-centric societal costs (i.e., non-medical costs reported in Table 4.11) and productivity gains, along with patient QALYs, LYs, and health care costs. Table 4.17 presents the results for Spinraza versus BSC comparison, while Table 4.18 presents the results for the Zolgensma versus BSC comparison.

The incremental cost per QALY and incremental cost per LY gained for Spinraza compared to BSC in the modified societal perspective were slightly less favorable than those in the health care perspective. This was because non-medical costs (which included moving or modifying the home and purchasing or modifying a vehicle), provided in Table 4.11, accrue for all the health states (except walking) for a lifetime, while patient productivity gains are only for patients sitting or walking between ages 25 and 67 years. As such, the productivity gains did not offset the non-medical costs for Spinraza in the SMA Type I population, as only around 19% of the patients in Spinraza arm were in the “sitting” health state and none were in the “walking” health state.

Table 4.17. Scenario Analysis Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	\$3,944,000	3.24	7.64	\$1,124,000	\$596,000
BSC	\$817,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

The incremental cost per QALY and incremental cost per LY gained for Zolgensma compared to BSC in the modified societal perspective were slightly more favorable than those in the health care perspective. In the Zolgensma arm, a majority of the patients were in the “sitting” health state and a proportion were in the “walking” health state, which resulted in the non-medical costs being offset by the productivity gains, leading to more favorable incremental cost-effectiveness ratios.

Table 4.18. Scenario Analysis Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$3,619,000*	12.23	18.17	\$238,000	\$178,000
BSC	\$817,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

Tables 4.19 and 4.20 present results from a scenario analysis from the health care sector perspective that excludes health care costs other than those directly related to treatment with Spinraza or Zolgensma (i.e., only treatment and administration costs). Table 4.19 presents the results for Spinraza versus BSC, while Table 4.20 presents the results for the Zolgensma versus BSC comparison.

The results for Spinraza compared to BSC in this scenario were more favorable than those in the base-case health care sector perspective, at \$810,000 per QALY gained and \$429,000 per LY gained.

Table 4.19. Scenario Analysis Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective Excluding Other Health Care Costs

	Drug Treatment Costs	Non-Treatment Health Care Costs*	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$21,154	\$2,252,000	3.24	7.64	\$810,000	\$429,000
BSC	\$0	\$0	\$0	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Administration costs associated with Spinraza.

In this scenario analysis, the total costs in the Zolgensma arm were approximately \$2 million, the assumed placeholder price for Zolgensma, because of one-time administration and the exclusion of background health care costs. This resulted in an incremental cost per QALY gained of \$170,000 and an incremental cost per LY gained of \$127,000.

Table 4.20. Scenario Analysis Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective Excluding Other Health Care Costs

	Drug Treatment Costs	Non-Treatment Health Care Costs*	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$137	\$2,000,000	12.23	18.17	\$170,000	\$127,000
BSC	\$0	\$0	\$0	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

We present the summary results for the other scenario analyses of Spinraza versus BSC comparison in Table 4.21, and the summary results for other scenario analyses of Zolgensma versus BSC comparison in Table 4.22. We present more detailed description of the assumptions behind each of these scenario analyses and detailed results in Appendix E (Tables E14 to E31). Note that there are no patients in the “walking” health state in the Spinraza arm, as such the assumptions about “walking” health state have no bearing on the Spinraza results, but to ensure consistency between Table 4.21 and 4.22, the scenarios describe assumptions about both “sitting” and “walking.” However, when describing the Spinraza results we only mention the assumptions about “sitting” health state.

In the scenario analyses for Spinraza versus BSC in Type I SMA patients, removing utility benefit for achieving interim milestones increased the incremental cost per QALY to \$1,303,000. Assuming lower health state costs resulted in more favorable incremental cost per QALY ratios. However, assuming lower survival or utilities for “sitting” health states resulted in less favorable incremental cost-effectiveness ratios. When both lower survival and utilities for the “sitting” health state are

used, the incremental cost per QALY gained was around \$1.4 million. This suggests that the base-case incremental cost per QALY is an underestimate if the patients achieving “sitting” do not do as well as SMA Type II patients.

If an increased proportion of patients in the “sitting” health state were to lose their milestones, the incremental cost-effectiveness ratios become less favourable (scenarios #7a-7c in Table 4.21). The conservative scenario which assumed that 30% of the patients in the “sitting” health state lose milestones and also assumed lower survival and lower utilities for those in the “sitting” health state, resulted in an incremental cost per QALY of approximately \$1.5 million and an incremental cost per LY gained of \$630,000. Note that the conservative scenario still includes the utility benefit for achieving interim milestones, as in the base case.

The scenario analyses using a 10-year time horizon resulted in an incremental cost per QALY of approximately \$1.5 million as the all the benefits for the patients in the “sitting” health state are not included. The scenario analyses using a discount rate of 1.5% for both costs and QALYs, resulted in an incremental cost per QALY of approximately \$1 million.

Table 4.21. Scenario Analyses for Spinraza versus BSC in Infantile-Onset (Type I) SMA

	Cost per QALY	Cost per LY
Base-Case Results	\$1,112,000	\$590,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	\$1,303,000	\$590,000
Scenario #2: Assuming Lower Health State Costs for “Not Sitting” and “Permanent Ventilation” Health States	\$990,000	\$525,000
Scenario #3: Assuming Lower Utilities for “Sitting” and “Walking” Health States	\$1,265,000	\$590,000
Scenario #4: Assuming Lower Survival for “Sitting” and “Walking” Health States	\$1,253,000	\$624,000
Scenario #5: Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States	\$1,407,000	\$624,000
Scenario #7a: Assuming 10% in “Sitting” Health State Lose Milestone at End of Short-Term Model	\$1,143,000	\$593,000
Scenario #7b: Assuming 20% in “Sitting” Health State Lose Milestone at End of Short-Term Model	\$1,178,000	\$597,000
Scenario #7c: Assuming 30% in “Sitting” Health State Lose Milestone at End of Short-Term Model	\$1,218,000	\$601,000
Conservative Scenario: Assuming 30% in “Sitting” Health State Lose milestone at End of Short-Term Model, Lower Utilities and Survival for “Sitting” and “Walking” Health States	\$1,509,000	\$630,000
Scenario #8: Using a 10-Year Time Horizon	\$1,460,000	\$700,000
Scenario #9: Using 1.5% Discount Rate for Both Costs and QALYs	\$1,052,000	\$566,000

LY: life-year, QALY: quality-adjusted life year

In the scenario analyses for Zolgensma versus BSC in infantile-onset (Type I) SMA patients, removing utility benefit for achieving interim milestones increased the incremental cost per QALY results to \$261,000. Assuming lower health state costs in the “not sitting” and “permanent ventilation” health states resulted in less favorable incremental cost per QALY ratios. Assuming lower survival or utilities for “sitting” and “walking” health states resulted in less favorable incremental cost-effectiveness ratios. When both lower survival and utilities for the “sitting” and “walking” health states are used, the incremental cost per QALY was \$371,000. This suggests that the base-case incremental cost per QALY is an underestimate if the patients in the “sitting” and “walking” health states do not do as well as SMA Type II patients and the general population.

If an increased proportion of patients in the “sitting” health state were to lose their milestones, the incremental cost-effectiveness ratios become less favorable (scenarios #7b-7c in Table 4.22). Scenario #7a is not presented, as our base case for Zolgensma arm already included 16.7% in the “sitting” health state losing milestone (as proxy for receiving Spinraza). The conservative scenario, which assumed that 30% of the patients in the “sitting” health state lose milestones and also

assumed lower survival and lower utilities for those in the “sitting” and “walking” health states, resulted in an incremental cost per QALY ratio of over \$400,000 and an incremental cost per LY gained of approximately \$250,000. Note that the conservative scenario still includes the utility benefit for achieving interim milestones, as in the base case.

The scenario analyses using a 10-year time horizon resulted in an incremental cost per QALY of approximately half a million as the all the treatment costs are included but the benefits for the patients in the “sitting” and “walking” health state are only for the 10 years. The scenario analyses using a discount rate of 1.5% for both costs and QALYs, resulted in an incremental cost per QALY of approximately \$200,000.

Table 4.22. Scenario Analyses for Zolgensma* versus BSC in Infantile-Onset (Type I) SMA

	Cost per QALY	Cost per LY
Base-Case Results	\$243,000	\$182,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	\$261,000	\$182,000
Scenario #2: Assuming Lower Health State costs for “Not Sitting” and “Permanent Ventilation” Health States	\$248,000	\$185,000
Scenario #3: Assuming Lower Utilities for “Sitting” and “Walking” Health States	\$296,000	\$182,000
Scenario #4: Assuming Lower Survival for “Sitting” and “Walking” Health States	\$303,000	\$233,000
Scenario #5: Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States	\$371,000	\$233,000
Scenario #6: Assuming No Loss of Milestones as a Proxy for Use of Spinraza in Zolgensma Arm	\$220,000	\$165,000
Scenario #7b: Assuming 20% in “Sitting” Health State Lose Milestone at End of Short-Term Model	\$249,000	\$186,000
Scenario #7c: Assuming 30% in “Sitting” Health State Lose Milestone at End of Short-Term Model	\$266,000	\$198,000
Conservative Scenario: Assuming 30% in “Sitting” Health State Lose milestone at End of Short-Term Model, Lower Utilities and Survival for “Sitting” and “Walking” Health States	\$406,000	\$253,000
Scenario #8: Using a 10-Year Time Horizon	\$525,000	\$400,000
Scenario #9: Using 1.5% Discount Rate for Both Costs and QALYs	\$199,000	\$149,000

LY: life-year, QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

Tables 4.23 and 4.24 present the results for a scenario analysis comparing Zolgensma with Spinraza from the health care sector and modified societal perspectives, respectively. Instead of a naïve

comparison that used the costs, QALYs, and LYs for Zolgensma and Spinraza from their respective comparisons with BSC, we performed a separate analysis incorporating the add on costs of Spinraza in the Zolgensma arm (as opposed to assuming that a proportion of the patients lose a milestone in the base-case analysis). This analysis assumed that 33% of the patients in the “sitting” state of the Zolgensma arm (i.e., 25% of overall patients) receive Spinraza according to the standard dosing regimen after the end of the short-term model.

From the health care sector perspective, the total costs in the Zolgensma arm were approximately \$5.3 million with 13.46 QALYs and 19.76 LYs gained. The costs are higher than in the base case for Zolgensma versus BSC due to the additional costs associated with Spinraza treatment. However, the QALYs and LYs are also higher than in the base case, as this analysis does not assume any loss of milestones. The total costs in the Spinraza arm were around \$3.9 million with 3.24 QALYs and 7.64 LYs gained. This resulted in an incremental cost per QALY gained of approximately \$139,000 and an incremental cost per LY gained of \$117,000 for Zolgensma compared to Spinraza.

Table 4.23. Scenario Analysis Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$3,630,000*	\$1,671,000	\$5,301,000	13.46	19.76	\$139,000	\$117,000
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of \$2 million) and additional Spinraza costs.

The results for the same comparison when taking a modified societal perspective are slightly lower than those in the health care perspective, with an incremental cost per QALY gained of \$129,000 and an incremental cost per LY gained of \$109,000. This was due to a greater proportion of patients in the “sitting” and “walking” health states for the Zolgensma arm than the Spinraza arm, resulting in more of the non-medical costs being offset by the patient productivity gains in the Zolgensma arm compared to Spinraza.

Table 4.24. Scenario Analysis Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$5,262,000*	13.46	19.76	\$129,000	\$109,000
Spinraza	\$3,944,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of \$2 million) and the additional Spinraza costs.

Threshold Analyses Results

Table 4.25 presents the threshold results for Spinraza and Zolgensma compared to BSC at thresholds from \$50,000 to \$500,000 per QALY gained, while excluding health care costs that may be considered “unrelated,” as described earlier.⁹³ While we understand that it may be controversial to treat these costs as unrelated, we thought it is important to explore the effect of excluding these costs from the analysis. As earlier, threshold prices are reported as annual costs for Spinraza and as one-time cost for Zolgensma.

Excluding these “unrelated” health care costs resulted in threshold prices at each cost per QALY threshold. For Spinraza, the annual threshold prices are \$44,000 and \$67,900 at thresholds of \$100,000/QALY and \$150,000/QALY, respectively. For Zolgensma, the one-time threshold prices are \$1,178,000 and \$1,767,000 at thresholds of \$100,000/QALY and \$150,000/QALY, respectively.

Table 4.25. QALY-Based Threshold Analyses Excluding “Unrelated” Health Care Costs in Type I SMA: Health Care Sector Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at \$50,000/QALY	\$20,200	\$589,000
Threshold Price at \$100,000/QALY	\$44,000	\$1,178,000
Threshold Price at \$150,000/QALY	\$67,900	\$1,767,000
Threshold Price at \$200,000/QALY	\$91,800	\$2,355,000
Threshold Price at \$300,000/QALY	\$139,000	\$3,533,000
Threshold Price at \$500,000/QALY	\$235,000	\$5,889,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Based on a placeholder price of \$2,000,000.

Table 4.26 presents the threshold price results for Spinraza and Zolgensma compared to BSC at thresholds from \$50,000 to \$500,000 per QALY gained (including “unrelated” health care costs). Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma.

Table 4.26. QALY-Based Threshold Analyses in Type I SMA: Health Care Sector Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at \$50,000/QALY	--	--
Threshold Price at \$100,000/QALY	--	\$310,000
Threshold Price at \$150,000/QALY	--	\$899,000
Threshold Price at \$200,000/QALY	--	\$1,488,000
Threshold Price at \$300,000/QALY	--	\$2,666,000
Threshold Price at \$500,000/QALY	\$90,000	\$5,021,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Based on a placeholder price of \$2,000,000.

Note that there are no threshold prices for Spinraza for thresholds of \$300,000/QALY and below because although more patients are alive in the Spinraza arm compared to BSC, only a proportion (around 19%) of the patients are in the “sitting” health state, with the rest in either “permanent ventilation” or “not sitting” health states; both of these health states have high costs of around \$300,000 per year and a low utility value of 0.19. As such, even at zero price for Spinraza, it is not possible for the incremental cost effectiveness ratios to reach thresholds less than \$300,000 per QALY. This phenomenon has been summarized in a NICE Decision Support Unit report.⁹³ As such, we have additionally reported the threshold prices for incremental costs per LY gained and for incremental cost per QALY gained excluding what may be considered as health state costs that are not related to the treatment *per se* (Tables 4.27 and 4.25, respectively).

Table 4.27 presents the threshold results for Spinraza and Zolgensma compared to BSC at thresholds from \$50,000 to \$500,000 per LY gained. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., costs of three doses]) and as a one-time cost for Zolgensma. As explained above, due to the majority of the patients in Spinraza arm being in “not sitting” and “permanent ventilation” health states, which are associated with high health care costs and low utility values, there are no threshold prices for Spinraza below thresholds of \$200,000 per LY gained.

Table 4.27. LYG-Based Threshold Analyses in Infantile-Onset (Type I) SMA: Health Care Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at \$50,000/LY	--	--
Threshold Price at \$100,000/LY	--	\$710,000
Threshold Price at \$150,000/LY	--	\$1,498,000
Threshold Price at \$200,000/LY	\$31,900	\$2,287,000
Threshold Price at \$300,000/LY	\$122,000	\$3,865,000
Threshold Price at \$500,000/LY	\$302,000	\$7,020,000

LY: life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Based on a placeholder price of \$2,000,000.

Later-Onset (Type II/III) SMA Model

Base-Case Results

Table 4.28 presents the base-case results from the health care sector perspective for the Spinraza versus BSC comparison. Note that no patients in either arm achieved the walking milestone (i.e., they were all in the “sitting” health state). In the CHERISH trial, one patient out of 84 in Spinraza arm managed to walk with assistance but was not considered to have achieved the “walking” health state in the base-case analysis. As such, Spinraza was dominated by BSC in cost/LY analyses, with higher costs but no increase in LYs. However, the QALYs are higher due to the inclusion of utility benefit for achieving interim milestones. This resulted in incremental cost effectiveness ratio of around \$8 million per QALY.

Table 4.28. Base-Case Results for Spinraza versus BSC in Later Onset SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$7,634,000	\$1,514,000	\$9,148,000	12.28	18.90	\$8,156,000	Dominated
BSC	\$0	\$1,442,000	\$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Sensitivity Analyses Results

One-way sensitivity analyses were not performed as all the parameters were the same in both arms, except for drug cost and the utility benefit for achieving interim milestones in the Spinraza arm, which was considered in scenario analyses. The incremental cost-effectiveness ratio did not change with any changes to other parameters, as any shifts affected both arms equally.

We performed probabilistic sensitivity analyses to understand effects of uncertainty on both costs and health outcomes, by varying input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges ($\pm 20\%$ of the mean). In the later onset SMA patients, Spinraza did not achieve a greater than zero likelihood of meeting the \$500,000/QALY or lower threshold across the range of values tested.

Scenario Analyses Results

Table 4.29 presents results from a scenario analysis taking a modified societal perspective, which includes patient-centric societal costs (i.e., non-medical costs) and productivity gains, along with health care costs. As above, Spinraza was dominated by BSC, with higher costs but no increase in LYs. However, the QALYs are higher due to the inclusion of utility benefit for achieving interim milestones. This resulted in an incremental cost effectiveness ratio of around \$8 million per QALY.

Table 4.29. Scenario Analysis for Spinraza versus BSC in Later-Onset SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	\$9,217,000	12.28	18.90	\$8,156,000	Dominated
BSC	\$1,510,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We performed additional scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results. We present the summary results for Spinraza versus BSC in Table 4.30. We present more detailed description of the assumptions behind each of these scenario analyses below and detailed results in Appendix E (Tables E36 to E38). Note that we do not present cost per LY results here as these scenarios have no impact on life expectancy and thus do not impact cost per LY.

In the first scenario, we assumed even greater additional utility benefits in the Spinraza arm for achieving interim milestones such as standing, walking with assistance, etc. This scenario assumed an even higher utility benefit for all patients in the “sitting” health states, implemented in the model as a utility of 0.7 for the “sitting” health state in the Spinraza arm (i.e., an additional utility of 0.1 compared to BSC).

In the second scenario, we assumed that Spinraza treatment was stopped after two years and applied a utility benefit for achieving interim milestones in the Spinraza arm (i.e., a utility of 0.65 for “sitting” health state in the Spinraza arm, an additional utility of 0.05 compared to BSC).

In the third scenario, we assumed that there is no utility benefit for achieving interim milestones which resulted in Spinraza being dominated by BSC, as it results in higher costs but same QALYs.

Table 4.30. Scenario Analyses for Spinraza versus BSC in Later Onset (Type II and III) SMA: Health Care Sector Perspective

	Cost per QALY
Base-Case Results	\$8,156,000
Scenario #1: Assuming Further Utility Benefits for Interim Milestones	\$4,078,000
Scenario #2: Assuming Utility Benefits for Interim Milestones and Stopping Spinraza after Two Years	\$1,204,000
Scenario #3: Assuming No Utility Benefits for Interim Milestones	Dominated

Threshold Analyses Results

Threshold analyses results were produced for the base-case analysis, but note that the results were based on assumed utility benefits for achieving interim milestones. No price exists for Spinraza at the \$50,000 per QALY threshold due to the marginal utility benefit and fixed administration costs of the drug. At other thresholds, Spinraza's price ranged from approximately \$1,100 annually at the \$100,000 per QALY threshold to approximately \$20,000 annually at the \$500,000 per QALY threshold, as seen Table 4.31.

Table 4.31. QALY-Based Threshold Analyses in Later-Onset SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at \$50,000/QALY	--
Threshold Price at \$100,000/QALY	\$1,100
Threshold Price at \$150,000/QALY	\$3,400
Threshold Price at \$200,000/QALY	\$5,800
Threshold Price at \$300,000/QALY	\$10,500
Threshold Price at \$500,000/QALY	\$20,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Presymptomatic SMA Model

Base-Case Results

Table 4.32 presents the base-case results from the health care sector perspective for the Spinraza versus BSC comparison in the presymptomatic SMA population, where we assumed that that 60% of patients had SMA Type I, 30% had SMA Type II, and 10% had SMA Type III. It should be noted that the results presented in this section relate to this specific split of SMA patients, and may not be generalizable if the proportions are different to those outlined above. The breakdown of LYs, QALYs, and costs according to health state for the different interventions are presented in Appendix Tables E39 to E42.

The total costs in the Spinraza arm were approximately \$12 million, approximately fifteen times the total costs in the BSC arm of approximately \$800,000. However, the Spinraza arm had more QALYs and LYs (21.94 and 26.58, respectively) compared to the BSC arm (6.25 QALYs and 9.51 LYs, respectively). This resulted in an incremental cost per QALY gained of \$709,000 and an incremental cost per LY gained of \$652,000 for Spinraza compared to BSC.

Table 4.32. Base-Case Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$10,565,000	\$1,364,000	\$11,929,000	21.94	26.58	\$709,000	\$652,000
BSC	\$0	\$801,000	\$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Sensitivity Analyses Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. The key drivers of uncertainty included monthly costs in the “walking” health state and the utility in the “sitting” health state (Figure 4.6 and Table 4.33). Spinraza did not achieve a greater than zero likelihood of meeting \$500,000/QALY or lower thresholds across the range of values tested (see Appendix E, Figures E9 and E10).

Figure 4.6. Tornado Diagram for Spinraza versus BSC in Presymptomatic SMA: Health Care Perspective

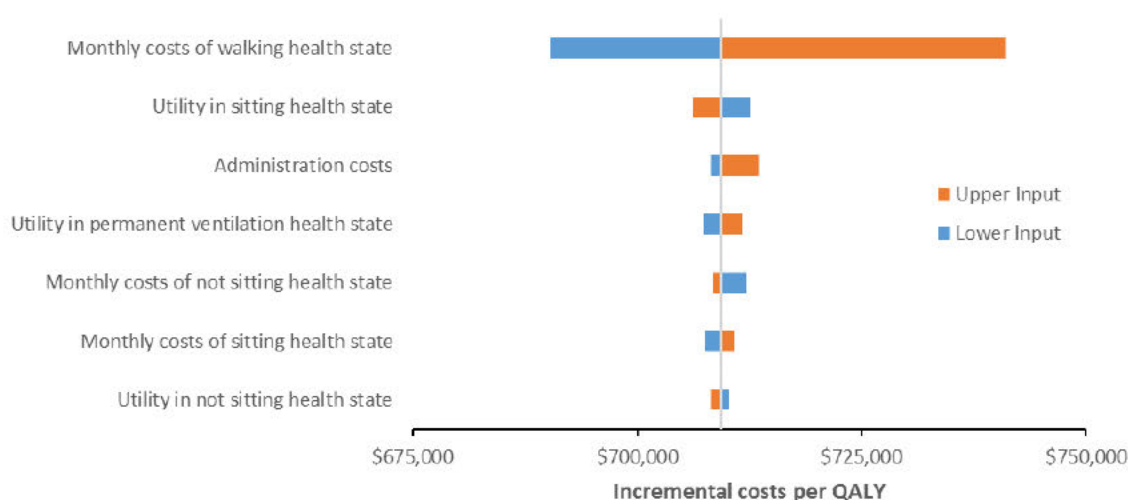


Table 4.33. Tornado Diagram Inputs and Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Monthly Costs of Walking Health State	\$690,000	\$741,000	\$1,000	\$5,000
Utility in Sitting Health State*	\$706,000	\$712,000	0.5	0.7
Administration Costs	\$708,000	\$713,000	\$1,000	\$2,000
Utility in Permanent Ventilation Health State	\$707,000	\$712,000	0.1	0.3
Monthly Costs of Not Sitting Health State*	\$708,000	\$712,000	\$10,434	\$30,000
Monthly Costs of Sitting Health State	\$707,000	\$711,000	\$3,000	\$9,000
Utility in Not Sitting Health State*	\$708,000	\$710,000	0.1	0.3

*Lower input corresponds to higher ICER and vice versa.

Scenario Analyses Results

Table 4.34 presents the results from a scenario analysis taking a modified societal perspective, which included patient-centric societal costs (i.e., non-medical costs) and productivity gains, along with patient QALYs and health care costs. The incremental cost per QALY and incremental cost per LY gained for Spinraza compared to BSC in this modified societal perspective were slightly more favorable than those in the health care sector perspective. In the Spinraza arm, a majority of the patients were in the “walking” health state and a proportion in the “sitting” health state, which resulted in the non-medical costs being offset by the productivity gains, leading to lower (more favorable) incremental cost-effectiveness ratios.

Table 4.34. Scenario Analysis for Spinraza versus BSC in Presymptomatic SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	\$11,559,000	21.94	26.58	\$687,000	\$632,000
BSC	\$773,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We performed several additional scenario analyses to identify the effects of alternative inputs and assumptions on the cost-effectiveness results in presymptomatic SMA. We present the summary results for the Spinraza versus BSC comparison in Table 4.35. We present more detailed description of the assumptions behind each of these scenario analyses and detailed results in Appendix E (Tables E43 to E49).

In the scenario analyses for Spinraza versus BSC in presymptomatic SMA patients, assuming no utility benefit for achieving interim milestones increased the incremental cost per QALY to \$727,000. Assuming lower health state costs resulted in lower (more favorable) incremental cost per QALY, as did assuming lower survival for the “sitting” and “walking” health states. However, assuming lower utilities for “sitting” and “walking” health states resulted in a higher incremental cost-effectiveness ratio of \$904,000 per QALY. This suggests that the base-case incremental cost per QALY is an underestimate if the patients’ utility in the “sitting” and “walking” health states are not as high as those in patients with SMA Type II and the general population, respectively.

Table 4.35. Scenario Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Cost per QALY	Cost per LY
Base-Case Results	\$709,000	\$652,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	\$727,000	\$652,000
Scenario #2: Assuming Lower Health State costs for “Not Sitting” and “Permanent Ventilation” Health States	\$712,000	\$655,000
Scenario #3: Assuming Lower Utilities for “Sitting” and “Walking” Health States	\$904,000	\$652,000
Scenario #4: Assuming Lower Survival for “Sitting” and “Walking” Health States	\$678,000	\$628,000
Scenario #5: Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States	\$877,000	\$628,000
Scenario #6: Using a 10-Year Time Horizon	\$890,000	\$870,000
Scenario #7: Using 1.5% Discount Rate for Both Costs and QALYs	\$679,000	\$612,000

LY: life-year, QALY: quality-adjusted life year

Scenario analyses were also conducted for a hypothetical drug (“Drug X”) treatment which had the one-time costs of Zolgensma with the health care costs, QALYs, and LYs associated with Spinraza in presymptomatic SMA patients.

The total costs in the Drug X arm were approximately \$3.3 million, which is around four times the total costs in the BSC arm of around \$800,000. However, the Drug X arm had higher QALYs and LYs (21.54 and 26.59, respectively) compared to the BSC arm (6.26 QALYs and 9.54 LYs, respectively). This resulted in an incremental cost per QALY gained of \$161,000 and an incremental cost per LY gained of \$145,000 for Drug X compared to BSC, as shown in Table 4.36.

Table 4.36. Hypothetical Drug X for Presymptomatic SMA: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	\$3,264,000	21.94	26.58	\$157,000	\$144,000
BSC	\$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Given the uncertainty involved with the long-term prognosis of presymptomatic population, we also performed scenario analyses for Drug X, assuming lower survival (approximately halving survival compared to estimates used in the base case) and lower utilities of 0.5 and 0.7 in “sitting” and “walking” health states, respectively. This resulted in an incremental cost per QALY gained of \$242,000 and an incremental cost per LY gained of \$174,000 for Drug X compared to BSC, as presented in Table 4.37.

Table 4.37. Hypothetical Drug X for Presymptomatic SMA Assuming Lower Survival and Utilities in “Sitting” and “Walking” Health States: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	\$2,984,000	13.21	20.19	\$242,000	\$174,000
BSC	\$615,201	3.43	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Threshold Analyses Results

Table 4.38 presents the threshold price results for Spinraza compared to BSC at thresholds from \$50,000 to \$500,000 per QALY. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]). For Spinraza compared to BSC in presymptomatic SMA patients, the annual threshold-based prices are around \$8,000 and \$264,000 at thresholds of \$50,000/QALY and \$500,000/QALY, respectively.

Table 4.38. Threshold Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at \$50,000/QALY	\$8,000
Threshold Price at \$100,000/QALY	\$36,400
Threshold Price at \$150,000/QALY	\$64,800
Threshold Price at \$200,000/QALY	\$93,200
Threshold Price at \$300,000/QALY	\$150,000
Threshold Price at \$500,000/QALY	\$264,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table 4.39 presents the threshold price results for Spinraza compared to BSC at thresholds from \$50,000 to \$500,000 per LY. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]). For Spinraza compared to BSC in presymptomatic SMA patients, the annual threshold-based prices are \$10,500 and \$289,000 at thresholds of \$50,000/LY and \$500,000/LY, respectively.

Table 4.39. Threshold Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at \$50,000/LY	\$10,500
Threshold Price at \$100,000/LY	\$41,400
Threshold Price at \$150,000/LY	\$72,300
Threshold Price at \$200,000/LY	\$103,000
Threshold Price at \$300,000/LY	\$165,000
Threshold Price at \$500,000/LY	\$289,000

LY: life-year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with specific input values (e.g., all set to 0, or all set to 1, etc.) to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs. We shared the model with AveXis for external verification. Biogen chose not to receive the model.

Model validation was also conducted in terms of comparisons to other published studies and analyses. We searched the literature to identify studies that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Published Evidence on Costs and Cost Effectiveness

In our review of prior economic models, we found no models comparing Zolgensma to other treatment options in patients with SMA. Key models included here are those submitted by the manufacturer of Spinraza to NICE¹³ and CADTH,⁹⁴ which compared Spinraza to BSC.

Two manufacturer-developed models submitted to NICE compared Spinraza to BSC in early-onset (Type I) and later-onset (Types II/III) SMA in the UK. This model was reviewed by an evidence review group (ERG) contracted by the Department of Health.¹³ Both the ICER and manufacturer-submitted models employed health states based on motor function milestones, but beyond the trial period, the ICER models assumed patients remained in the same health state as at end of trial, while the manufacturer models extrapolate the trial-derived transition probabilities (using CHOP-INTEND scores) beyond the trial period. As highlighted by the ERG and noted by the review committee, this extrapolation was favorable to Spinraza, in that patients receiving Spinraza could not worsen over time, but only improve or remain stable in each cycle, while patients in the BSC arm could not improve over time but could only worsen or stay within the same health state. Another important difference is that the manufacturer-submitted models did not include permanent ventilation as a health state, while the ICER models do. The manufacturer-submitted Type I model included Spinraza discontinuation at 13 months even if patients were able to sit, based on the ENDEAR trial, while the ICER model extends Spinraza duration for up to 24 months before discontinuation among patients who achieved no improvement in milestones, based on the SHINE extension trial. The manufacturer-submitted models included scoliosis surgery and subsequent Spinraza discontinuation, while the ICER models do not include scoliosis surgery. We are unable to compare utility values between the manufacturer-submitted and ICER models since the former models' utility inputs remain confidential. We do not compare the costs of Spinraza, BSC, and other health care costs in the different sets of models, due to the very different cost structures between the US and the UK.

Comparing outcomes in the SMA Type I model, the manufacturer-submitted models produced 7.86 and 2.49 QALYs for Spinraza and BSC, respectively, in the base case. However, NICE commented in bold that: *“The company’s transition probabilities are optimistic and do not reflect clinical practice.”*; *“The modelled long-term overall survival benefit is based on optimistic assumptions and is highly uncertain”*; and that *“Utility values in the economic model are highly uncertain.”* Further details are provided in their Appraisal Consultation Document.¹³ The ICER model resulted in 3.24 and 0.46 QALYs for Spinraza and BSC, respectively. The difference in QALYs gained between the manufacturer-submitted and the ICER models are being driven primarily by assumptions relating to long-term treatment outcomes, the baseline patient health state distributions, and the lack of

permanent ventilation as an outcome in the manufacturer-submitted model. Using either the manufacturer-submitted models or the ERG's modifications to the manufacturer-submitted model resulted in incremental cost-effectiveness ratios for Spinraza ranging from approximately £400,000 per QALY to approximately £630,000 per QALY.

The SMA Type II/III model submitted by the manufacturer to NICE resulted in 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case subject to the limitations described by NICE. The ICER model resulted in 12.28 and 11.34 QALYs for Spinraza and BSC, respectively, in the base-case analysis. Using either the manufacturer-submitted models or the ERG's modifications to the manufacturer-submitted model resulted in incremental cost-effectiveness ratios for Spinraza ranging from being dominated to approximately £1.25 million per QALY. In the ICER model's base case and modified societal perspective analyses, Spinraza had a cost-effectiveness ratio of a little over \$8 million per QALY.

Similar models for Spinraza were submitted by the manufacturer to CADTH's Common Drug Review (CDR).⁹⁴ Some of the key differences between the NICE and CADTH models were separation of the Type II/III models into separate models for Type II and Type III, a change in the modeled time horizon, and use of a 1.5% discount rate versus 3.5%. The CDR raised similar concerns with the manufacturer-submitted models as those raised by the ERG in the NICE appraisal. Key concerns included continued treatment benefit in the Spinraza arm beyond the trial duration, the use of unpublished utility estimates, initial state probabilities based on trial-specific distribution of patients by motor function milestones achieved, and uncertainty around mortality estimates for SMA Types I and II. The manufacturer-submitted model showed health outcomes (QALYs) in SMA Types I, II, and III for Spinraza versus BSC as 3.92 versus -0.88, 23.28 versus 19.60, and 12.05 versus 10.49, respectively. Incremental cost-effectiveness ratios for the SMA Type I, II, and II models were estimated at approximately \$670,000 per QALY, \$2.1 million per QALY and \$2.8 million per QALY, respectively. The CDR reanalyzed the manufacturer-submitted model, making modifications to it such as including published utilities, assuming no continued benefit of Spinraza beyond trial duration, and changes to mortality estimates. These modifications resulted in substantially lower QALY gains for Spinraza and subsequently higher incremental cost-effectiveness ratios, at approximately \$9.2 million per QALY, \$24.4 million per QALY and \$7.4 million per QALY for SMA Types I, II, and III, respectively.

Limitations

Our analyses have important limitations. Most of these relate to the lack of availability of robust data and the assumptions required to overcome this. There is no long-term follow-up for either treatment, resulting in considerable uncertainty related to the prognosis of patients with SMA. We used motor function milestones to define broad health states and had to assume relationships between these motor function milestone-based health states and survival. Uncertainty in long-term survival was partially accounted for in sensitivity and scenario analyses that evaluated

different assumptions. As there are no long-term data on the extrapolation of motor function milestones, the base-case analyses assume that these are sustained until death. However, we performed conservative scenario analyses assuming a proportion of the patients in the “sitting” health state lose their milestones.

Furthermore, relevant interim milestones could not be included in the model, as these data were not available for all the treatments. However, the base-case analyses included utility benefit in the treatment arms compared to BSC to make allowances for better functioning in treatment arms within these broad health states.

For Spinraza in presymptomatic SMA patients and for Zolgensma in SMA Type I patients, the evidence was based on single-arm studies. Thus, the uncertainty produced from this analysis likely underestimates the total uncertainty involved. We could not estimate disease progression parameters (e.g., transition probabilities) without access to individual patient data from the studies. As such, the data for the different interventions during the study period were used directly in the model to estimate short-term costs/QALYs. This is subject to limitations, especially towards the end of the follow up period, where survival probabilities remain constant for an extended period of time due to small numbers at risk and the censoring involved. However, this methodology does have the advantage of matching the study data, subject to the caveat related to naïve comparisons due to single-arm studies.

There were some structural assumptions in the model. While the survival of those who are in “permanent ventilation” at the end of the short-term model is included, the mortality of the patients that transition to the “permanent ventilation” state from the “not sitting” health state is not modelled explicitly in the long-term model. However, additional costs for permanent ventilation were included for three months prior to death in the “not sitting” state.

There is no explicit discontinuation of Spinraza treatment in the later onset SMA and presymptomatic SMA models. In the SMA Type I model, the patients in the Spinraza arm who were in “permanent ventilation” and “not sitting” health states were assumed to stop treatment after 24 months.

Robust utility data were lacking for these populations, with many identified studies lacking face validity. As such, we used utility data derived from several sources that were believed to be coherent. The base-case analyses were complemented with sensitivity and scenario analyses to explore the uncertainty in these values. Similarly, cost data were lacking, requiring several assumptions to be made. Importantly, the cost of Zolgensma is unknown. These uncertainties were partially addressed through altering the cost inputs in sensitivity analyses, as well as presenting threshold-based price ranges. However, due to the lack of data, the distributions used for costs and utilities in the PSA are on mean values $\pm 20\%$. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses.

Given the nature of SMA, it is difficult to disentangle the adverse events due to treatment from the complications associated with SMA itself, which are already accounted for in the health state costs and disutilities. As such, the costs and disutilities of adverse events were not included in the model.

Finally, our analyses using a modified societal perspective do not include quality of life burden associated with caregivers, as the methods for performing economic evaluations including such caregiver burden are still under development. Incorporating caregiver burden may lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer. Furthermore, there is a lack of data on utilities and lost income for caregivers of patients with SMA. As such, we present our thinking on these considerations in Appendix E (Tables E8 and E9) but we do not present results of the analyses using modified societal perspective including caregiver burden.

Conclusions

Spinraza appears to be most cost effective when used in patients with presymptomatic SMA. In this population, the estimated incremental cost-effectiveness of Spinraza is \$709,000 per QALY gained from a health care sector perspective and \$687,000 from a modified societal perspective, far exceeding usual cost-effectiveness thresholds. The estimated cost per LY gained in this setting is \$652,000 from the health care sector perspective and \$632,000 from the modified societal perspective. For Zolgensma (at a placeholder price of \$2 million) the estimated incremental cost-effectiveness from a health care sector perspective in patients with symptomatic Type I SMA is \$243,000 per QALY gained and the estimated cost per LY gained is \$182,000; the results were very similar from a modified societal perspective.

4.4 Summary and Comment

We have presented multiple analyses of Spinraza and Zolgensma to address considerations including:

- Different patient populations (symptomatic/presymptomatic; Type I, Type II/III SMA)
- Value of survival in a health state with poor quality of life
- Difficulties in finding a price to meet commonly cited willingness-to-pay thresholds when background medical treatment costs are extremely high

For Spinraza, our base-case results found that, at its current price, it does not meet traditional cost-effectiveness thresholds in any population of use. Spinraza, as used in its randomized trial in symptomatic Type I SMA, prolonged the lives of some children who were on permanent ventilation or unable to sit. These children have very high health care costs, and so a drug with these characteristics may not appear cost-effective at any price. Using suggested guidance regarding this circumstance,⁹³ we performed an analysis where we excluded “unrelated” health care costs. In this

analysis, the incremental cost-effectiveness of Spinraza was \$810,000 per QALY and \$429,000 per LY gained, still exceeding usual cost-effectiveness thresholds. Even when used in a presymptomatic population, where cost-effectiveness results were most favorable, Spinraza's price would need to be reduced below \$65,000 per year to meet a \$150,000 per QALY threshold. For later-onset SMA the incremental cost-effectiveness of Spinraza was over \$8 million per QALY gained, as current evidence did not demonstrate life extension and the benefits of treatment translate to small improvements in quality of life compared to best supportive care.

For Zolgensma at a placeholder price of \$2 million, our base-case results found that it too does not meet traditional cost-effectiveness benchmarks for use for patients with Type I SMA and would have to have its price reduced to under \$900,000 for the one-time administration to meet a \$150,000 per QALY threshold. Although we present a scenario analysis that allows Zolgensma to offset costs of Spinraza, we do not consider this a suitable base case for the purposes of determining long-term value for money or as the basis of a value-based price recommendation. Spinraza is relatively new and our analyses suggest it is not cost effective at commonly-cited usual thresholds. Additionally, it is important to recognize that the evidence for Zolgensma in this setting is based on 12 patients, while the evidence for Spinraza comes from a randomized trial with over 100 patients. As in prior reports, we feel it is inappropriate for a therapy to appear cost effective simply by offsetting costs of a recently introduced very expensive alternative. In this scenario, at a placeholder price of \$2 million, the incremental cost-effectiveness of Zolgensma from a health care sector perspective was \$139,000 per QALY and \$117,000 per LY gained. Policymakers will have the results of the Zolgensma versus Spinraza modeling to support their own judgment of value.

In order to provide policymakers with a broad view of cost-effectiveness, we also examined costs per LY gained. This approach values any life extension, even at a very low quality of life, as equal to life extension at full health. Cost per LY gained does not capture improvements in quality of life as intended by ICER's stated goal of highlighting an "equal value for life-year gained" (evLYG) measure, but in this case it was not possible to construct this measure, and viewing results of both the cost per LYG and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group. For Spinraza in presymptomatic SMA, we estimated the cost per LYG as \$652,000 from the health care sector perspective. For Zolgensma in patients with symptomatic Type I SMA, at a placeholder price of \$2 million the corresponding finding in the health care sector analysis was \$182,000 per LYG. In this analysis, Zolgensma's price would need to be approximately \$1.5 million to meet a \$150,000 per LYG threshold. We performed multiple additional sensitivity and scenario analyses to address multiple avenues of uncertainty. We conducted numerous scenario analyses to explore questions about the best way to model the connection between motor skill improvements and quality of life, the impact of different time horizons and of a societal perspective on modeling results, and the relevance of substantial non-drug health care costs that continue to accrue when a treatment extends life. Except for one scenario analysis, which took a 10-year time horizon, we assumed in all

other analyses that the short-term benefits of both treatments persist for a lifetime. Although there remains substantial uncertainty about whether this will prove true, input from clinical experts and judgments based on the mechanism of action of the two treatments leads us to believe that our base-case assumption of lifetime durability of benefit, while it may be viewed as optimistic by some, is the best starting point for a judgment of the value of these treatments at this time.

For Spinraza, when accounting for model input uncertainty through scenario and one-way sensitivity analyses, the incremental cost effectiveness ratios did not fall below \$670,000 per QALY gained. The results were most sensitive to the length of survival, the costs associated with treating people with SMA, and the utilities in both the “sitting” and “not sitting” health states. Results from the probabilistic sensitivity analyses found that Spinraza had a zero likelihood of achieving cost-effective thresholds of less than \$500,000 per QALY gained.

For Zolgensma, when accounting for model input uncertainty through scenario and one-way sensitivity analyses the range in the incremental cost-effectiveness ratios was \$199,000 to \$406,000 per QALY gained. The results were most sensitive to the length of survival, health care costs, and utility in both the “sitting” and “walking” health states. Results from the base-case probabilistic sensitivity analysis found that Zolgensma had a 0.1% chance of being cost effective at thresholds of \$150,000 per QALY but 100% chance of being cost-effective at thresholds above \$300,000 per QALY gained.

Among the most challenging aspects of this cost-effectiveness analysis has been uncertainty about the future clinical use of these treatments. Will they be used primarily for presymptomatic patients? With data demonstrating effectiveness of Spinraza in this population, this evolution seems quite likely, a judgment confirmed by input from clinical experts. For Zolgensma the future is less clear due to the fact that it has not yet been studied in presymptomatic patients. But with the possibility of its use in this population we decided to create a hybrid “Drug X” that had the placeholder cost of Zolgensma and the effectiveness of Spinraza in this population. Given that Drug X is administered as a one-time infusion, we found its cost-effectiveness very near traditional ranges assuming a placeholder price of \$2 million. There is obviously substantial uncertainty in the potential effectiveness of Zolgensma in the presymptomatic population, but our hypothetical Drug X results may serve as a starting point for policy debates should the FDA approval language suggest that Zolgensma may be used in this population even without supporting clinical data.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and the subsequent text provides detail about some elements that are relevant to Spinraza and Zolgensma compared with supportive care.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
This intervention will have a significant positive impact outside the family, including communities.
This intervention will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
There is significant uncertainty about the long-term risk of serious side effects of this intervention.
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

As discussed in Section 1, SMA is a condition of particularly high severity and rapid progression, with the most severe cases affecting infants and young children.^{1,2} In the most common and severe form of SMA, estimates of the median age at death range from 10.4 months up to four years.^{30,48,49} Survival depends on respiratory function, and many infants and children become permanently

ventilated. Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary, supportive care is needed. Supportive care does not modify disease progression, and patients may be entirely dependent on family members who expend intense emotional and physical effort when constantly caring for a patient. Hence, SMA may affect the health-related quality of life of patients as well as their families, caregivers, and wider communities.

Spinraza is the first FDA approved treatment that modifies disease progression. The availability of a disease-modifying treatment has paved the way for newborn screening. A federal recommendation to screen SMA in newborns was approved in July 2018, and several states have decided to adopt or pilot test SMA newborn screening since then.^{45,46}

Zolgensma is a one-time, intravenous administration which may reduce complexity and reduce caregiver burden compared with repeated lumbar punctures. As a one-time administration, there may also be reduced complexity for patients and caregivers navigating insurance policies.

Both interventions may have benefits beyond the outcomes assessed in trials. For example, if treatment improves or retains children's mobility, children may attend school and caregivers may return to work. An effective treatment also may reduce anxiety and stress among caregivers and wider communities, reduce other resources used (e.g., in schools), and promote more interaction between children with SMA and others in the community. Furthermore, for some patients and families, retaining current function is a meaningful outcome, and small improvements in motor abilities can allow patients greater ability for self-care and independence.

Overall, the existing evidence on Spinraza (SMA Types I-III) or Zolgensma (SMA Type I) suggested that treatment prolonged survival and improved motor functioning compared with historical cohorts or sham controls. At this time, data on presymptomatic patients with SMA and on longer-term durability and tolerability in symptomatic patients are limited. Additional data from open-label extensions and other future studies will help provide insights on long-term potential benefits and harms of treatments, on which uncertainty remains.

6. Value-Based Price Benchmarks

Our value-based price benchmarks for Spinraza and Zolgensma are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY gained. We note that for treatments of ultra-rare disorders, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than those applied to decisions about other treatments.

For Spinraza, the value-based benchmark price was estimated in the presymptomatic SMA population. Spinraza showed the most benefits in this population, and SMA has been added to the Recommended Uniform Screening Panel for newborns in the US,¹² making it likely that many patients will be identified and treated before symptoms develop. For Zolgensma, the value-based benchmark price was estimated in the SMA Type I population as currently data are not available for presymptomatic treatment with Zolgensma.

Value based prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma.

Table 6.1 Value-Based Benchmark Prices of Spinraza and Zolgensma

	List Price + Estimated Mark-Up	Population	VBP at \$100,000 per QALY Threshold	VBP at \$150,000 per QALY Threshold	Discount Required to Achieve Threshold Prices
Spinraza	\$382,500	Presymptomatic SMA	\$36,400*	\$64,800*	83% to 90%
Zolgensma	\$2,000,000†	Infantile-Onset (Type I) SMA	\$310,000	\$899,000	N/A as real-world price is unknown

QALY: quality-adjusted life year, VBP: value-based benchmark price

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+. Year one value-based benchmark prices are \$72,800 to \$129,400 due to the required loading doses.

†Placeholder price.

We are increasing reference to the cost per LYG figures to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which Spinraza meets the \$100,000 to \$150,000 per LYG range for use in presymptomatic patients is \$41,400 to \$72,300. This range is quite similar to the cost per QALY range. For Zolgensma, however, there is notable difference. The relevant cost per LYG price range for Zolgensma when used for Type I SMA is \$710,000 to \$1,498,000 for the \$100,000 to \$150,000 per LYG thresholds.

Broader Threshold Price Analyses

Table 6.2 presents the threshold price results for Spinraza compared to BSC for presymptomatic individuals at thresholds from \$50,000 to \$500,000 per QALY gained and per LY gained. Threshold prices are reported as annual costs for Spinraza, including administration fees.

Table 6.2. Threshold Prices for Spinraza in Presymptomatic SMA

	Per QALY*	Per LYG*
Threshold Price at \$50,000/QALY	\$8,000	\$10,500
Threshold Price at \$100,000/QALY	\$36,400	\$41,400
Threshold Price at \$150,000/QALY	\$64,800	\$72,300
Threshold Price at \$200,000/QALY	\$93,200	\$103,000
Threshold Price at \$300,000/QALY	\$150,000	\$165,000
Threshold Price at \$500,000/QALY	\$264,000	\$289,000

LYG: life-year gained, QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table 6.3 presents the threshold price results for Zolgensma compared to BSC in Type I SMA at thresholds from \$50,000 to \$500,000 per QALY gained and per LY gained. Threshold prices are reported for the one-time cost for Zolgensma.

Table 6.3. Threshold Prices for Zolgensma in Type I SMA

	Per QALY*	Per LYG*
Threshold Price at \$50,000	--	--
Threshold Price at \$100,000	\$310,000	\$710,000
Threshold Price at \$150,000	\$899,000	\$1,498,000
Threshold Price at \$200,000	\$1,488,000	\$2,287,000
Threshold Price at \$300,000	\$2,666,000	\$3,865,000
Threshold Price at \$500,000	\$5,021,000	\$7,020,000

LYG: life-year gained, QALY: quality-adjusted life year

*Based on a placeholder price of \$2,000,000.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of Zolgensma in patients diagnosed with SMA Type I in the US. Because no published evidence exists that can inform an economic evaluation of this therapy in presymptomatic or in Type II/III SMA patients, we restricted our budget impact to only SMA Type I patients. We used the assumed placeholder price and the threshold prices calculated using our base-case QALY results for Zolgensma (Table 4.25) in our estimates of budget impact. We did not estimate the budget impact of Spinraza because it has already been in use in the US marketplace for over a year.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total net cost of using Zolgensma compared with BSC only for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. In a separate scenario, we also examined the potential budget impact of use of Zolgensma compared with a mix of Spinraza and BSC in that population. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

To estimate the eligible population, we first identified the incidence of SMA in the US. The incidence was assumed to be the US SMA birth prevalence (9.4 per 100,000 live births) as estimated by Lally et al.³ We then applied this estimate to the most recent, published data on the number of live births in the US, to estimate the number of new cases of SMA in the US each year.⁹⁵ The distribution of type-specific birth prevalence indicates that approximately 58% of all SMA cases are Type I.⁹⁶ Applying these estimates to the projected 2019 to 2023 US population⁹⁷ resulted in an average of 215 new SMA Type I patients eligible to be treated with Zolgensma each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere⁹⁸ and have been [recently updated](#). The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately \$991 million per year for new drugs.

To estimate potential budget impact, we evaluate a new therapy that would take market share from one or more existing therapies/treatments and calculate the blended budget impact

associated with displacing use of existing therapies with the new intervention. For this analysis, we evaluated the potential budget impact of using Zolgensma compared to BSC only for SMA treatment. In a separate scenario analysis for Zolgensma, we assumed that most of the incident patients would have received the treatment currently on the market (i.e., Spinraza) in the absence of Zolgensma. We therefore assumed that, in the absence of Zolgensma, 75% of patients would initiate treatment with Spinraza while 25% would receive BSC. In light of a July 2018 federal recommendation that all newborns be screened for SMA and several states subsequently deciding to adopt or pilot test SMA newborn screening,^{45,46} we included an additional scenario analysis where we assumed all incident SMA patients would be treated with Spinraza in place of BSC. We used Spinraza's current net price (including hospital mark-up) for this scenario. Since current published trial evidence in the presymptomatic SMA patient group is limited to Spinraza, we did not consider Zolgensma for this scenario. We estimated this incident population size at approximately 370 patients per year.

7.3 Results

Table 7.1 illustrates the per-patient budget impact calculations of Zolgensma, based on the assumed placeholder price (\$2 million per one-time treatment) and the prices to reach \$150,000 and \$100,000 per QALY for Zolgensma (\$899,000 and \$310,000, respectively), compared to BSC only. Note that because of high background costs, there was no price of Zolgensma that achieved an incremental cost effectiveness ratio of \$50,000 per QALY.

Table 7.1. Per-Patient Budget Impact Calculations for Zolgensma Compared to BSC Only, Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	\$150,000/QALY	\$100,000/QALY
Zolgensma*	\$1,113,600	\$610,800	\$341,900
BSC	\$167,400		
Difference	\$946,300	\$443,500	\$174,500

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

All costs rounded to the nearest \$100.

*Based on a placeholder price of \$2,000,000.

The average potential budgetary impact compared to BSC only when using the assumed placeholder price was an additional per-patient cost of approximately \$946,300. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately \$443,500 per patient using the annual price to achieve \$150,000 per QALY to approximately \$174,500 per patient using the annual price to achieve a \$100,000 per QALY cost-effectiveness threshold.

The annual potential budgetary impact of treating the entire eligible population with Zolgensma rather than BSC only did not exceed the \$991 million threshold across all three prices, reaching 45% of the threshold at the assumed placeholder price of \$2 million (Table 7.2), largely due to the relatively small number of patients eligible for treatment. The potential budget impact would be even lower at the two threshold prices.

Table 7.2. Estimated Total Potential Budget Impact (BI) of Zolgensma* Treatment Compared to BSC Only, Using Different Prices Over a Five-Year Time Horizon, Assuming 215 Eligible Patients per Year

	Zolgensma*: Percent of Threshold
Assumed Placeholder Price	45%
\$150,000 per QALY Threshold Price	21%
\$100,000 per QALY Threshold Price	8%

*Based on a placeholder price of \$2,000,000.

Scenario Analysis Compared to Spinraza/BSC Mix

Table 7.3 illustrates the per-patient budget impact calculations, based on the assumed placeholder price (\$2 million per one-time treatment) and the prices to reach \$150,000 and \$100,000 per QALY for Zolgensma, compared to a 75%/25% mix of Spinraza/BSC. As before, because of high background costs, there was no price of Zolgensma that achieved an incremental cost effectiveness ratio of \$50,000 per QALY.

Table 7.3. Per-Patient Budget Impact Calculations for Zolgensma Compared to Spinraza/BSC (75%/25%), Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	\$150,000/QALY	\$100,000/QALY
Zolgensma*	\$1,113,600	\$610,800	\$341,900
Spinraza/BSC (75%/25%)	\$540,600		
Difference	\$573,100	\$70,300	-\$198,700†

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

All costs rounded to the nearest \$100.

*Based on a placeholder price of \$2,000,000.

†Cost-saving.

In this case, the average potential budgetary impact when using the assumed placeholder price was an additional per-patient cost of approximately \$573,100. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately \$70,300 per patient using the annual price to achieve \$150,000 per QALY to saving approximately \$198,700 per patient using the annual price to achieve a \$100,000 per QALY cost-effectiveness threshold.

The annual potential budgetary impact of treating the entire eligible population with Zolgensma rather than a mix of Spinraza/BSC did not exceed the \$991 million threshold across all three prices, reaching only 24% of the threshold at the assumed placeholder price of \$2 million (Table 7.4), again due to the relatively small number of patients eligible for treatment. Furthermore, Zolgensma treatment was estimated to be cost-saving at the \$100,000 per QALY threshold price, mainly due to the high costs associated with the comparator (75%/25% mix of Spinraza/BSC).

Table 7.4. Estimated Total Potential Budget Impact (BI) of Zolgensma* Treatment Compared to Spinraza/BSC (75%/25%), Using Different Prices Over a Five-Year Time Horizon, Assuming 215 Eligible Patients per Year

	Zolgensma*: Percent of Threshold
Assumed Placeholder Price	24%
\$150,000 per QALY Threshold Price	1%
\$100,000 per QALY Threshold Price	-12%†

*Based on a placeholder price of \$2,000,000.

†Cost-saving.

Scenario Analysis Comparing Spinraza to BSC in Pre-symptomatic SMA Patients

In this scenario, the average annual potential budgetary impact of using Spinraza relative to BSC in the pre-symptomatic SMA patient group was approximately \$573,900. The annual potential budgetary impact of treating this entire eligible population with Spinraza reached 58% of \$991 million annual threshold at its current net price.

This is the first ICER review of Spinraza and Zolgensma.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item	Section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	N/A
ABSTRACT			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1.1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1.2
METHODS			
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3.2
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	1.2
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3.2
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3.2
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	1.2
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3.2
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3.2
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.3
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3.3, Appendix D
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3.3, Appendix D
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3.3
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3.3
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	3.5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3.4, 3.5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	3.4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page iii

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

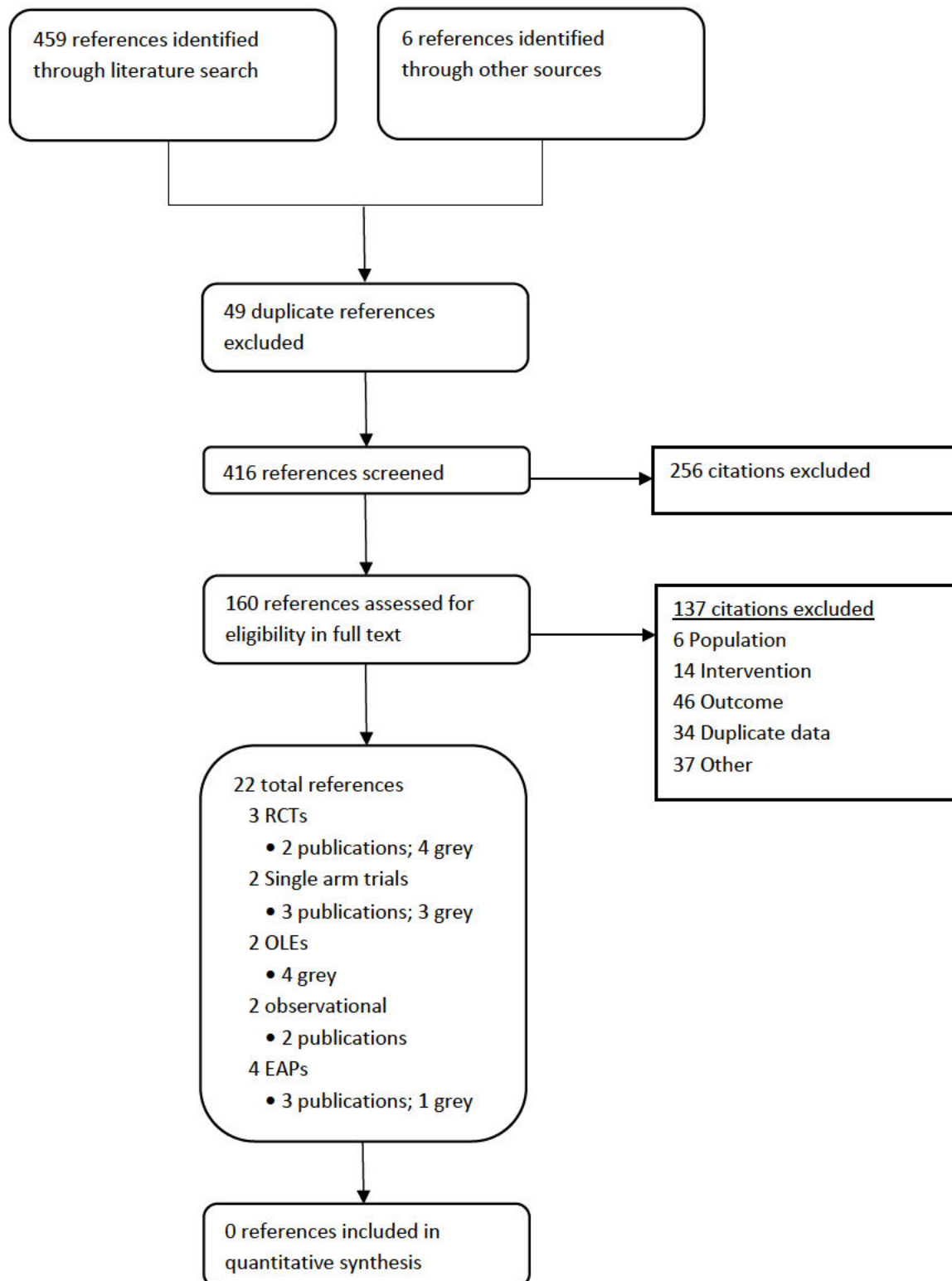
Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Using OVID)

No.	Search Terms
1	exp spinal muscular atrophy
2	Werdnig Hoffman.mp.
3	Kugelberg Welander.mp.
4	Spinraza.mp.
5	ISIS\$396443.mp.
6	AVXS\$101.mp.
7	Zolgensma.mp.
8	OR/1-3
9	OR/4-7
10	8 AND 9
11	(animals not (humans and animals)).sh.
12	10 not 11
13	(addresses or autobiography or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
14	12 not 13
15	limit 14 to English language

Table A3. Search Strategy of EMBASE SEARCH

No.	Search Terms
#1	'spinal muscular atrophy'
#2	'werdnig hoffmann disease'
#3	'kugelberg welander disease'
#4	#1 or #2 or #3
#5	'Zolgensma'
#6	'avxs 101'
#7	'Spinraza'
#8	'spinraza'
#9	'ISIS 396443'
#10	'antisense oligonucleotide'
#11	'gene therapy'
#12	#5 or #6 or #7 or #8 or #9 OR #10 or #11
#13	#4 AND #12
#14	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#15	'human'/exp
#16	#14 AND #15
#17	#14 NOT #16
#18	#13 NOT #17
#19	#18 AND [english]/lim
#20	#19 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#21	#19 NOT #20

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Spinraza and Zolgensma for Spinal Muscular Atrophy



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified one systematic review of Spinraza for the treatment of SMA Types I, II, and III, summarized below.

CADTH (2018). Spinraza (Spinraza) Clinical Review Report.⁹⁹ CADTH Clinical Review Report.

CADTH conducted a systematic review to evaluate current treatments available for SMA. Only one trial met their criteria for a systematic review: the ENDEAR study (CS3B), a randomized, double-blind, sham-controlled, multi-center study. One hundred and twenty-one patients were randomized 2:1 to receive either Spinraza (n=80) or placebo (n=41). The primary outcome of this study was the Hammersmith Infant Neurological Examination (HINE). Patients received either 12 mg of Spinraza intrathecally through lumbar puncture with four loading doses on days 0, 14, 28 and 63 with maintenance doses every four weeks or a matched sham injection. Interim analysis showed that patients in the Spinraza group showed improvement in motor function milestones, as measured by the HINE scale, versus that of the placebo group (difference in percentage=50.7, p-value<0.0001). As a result of the statistical significance in HINE scores, the trial was ended early.

Appendix C. Ongoing Studies

Title/Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Onasemnogene Apeparvovec					
Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type I AveXis, Inc. <u>NCT03461289</u>	Phase III, open-label, single-arm, single-dose trial Estimated Enrollment: 40	<u>Intervention:</u> AVXS-101	<u>Inclusion Criteria</u> Patients with SMA Type I Patients <6 months of age Swallowing evaluation <u>Exclusion Criteria</u> Previous, planned, expected scoliosis surgery Use of invasive ventilation support Use of requirement of 12+ hours of non-invasive ventilation support Patient with signs of aspiration Participation in recent SMA treatment clinical trial	<u>Primary Outcomes</u> Sitting without support up 18 months of age <u>Secondary Outcomes</u> Survival	November 2020

Title/Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Long-term follow up study for Patients from AVXS-101-CL-101 AveXis, Inc. NCT03421977	Observational Estimated Enrollment: 15	<u>Intervention:</u> AVXS-101	<u>Inclusion Criteria</u> Patient who received AVXS-101 in the AVXS-101-CL-101 Gene replacement therapy Clinical trial for SMA Type I Parent/Legal guardian willing and able to complete informed consent process <u>Exclusion Criteria</u> Parent/legal guardian unable or unwilling to participate in long term follow up safety procedure	<u>Primary Outcomes</u> Long-term safety	December 2023

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type I (STR1VE) AveXis, Inc. NCT03306277	Phase III, open-label, single-arm Estimated Enrollment: 20	<u>Intervention:</u> AVXS-101	<u>Inclusion Criteria</u> Patient who received avxs-101 in the AVXS-101-CL-101 Gene replacement therapy Clinical trial for SMA Type I Parent/Legal guardian willing and able to complete informed consent process <u>Exclusion Criteria</u> Parent/legal guardian unable or unwilling to participate in long term follow up safety procedure	<u>Primary Outcomes</u> Achievement of independent sitting Event-free survival <u>Secondary Outcomes</u> Ability to thrive Ventilatory support independence	March 31, 2020
Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for patients with Multiple Copies of SMN2 (SPR1NT) AveXis, Inc. NCT03505099	Phase III, open-label, single arm study Estimated Enrollment: 44	<u>Intervention:</u> AVXS-101 One-time intravenous fusion of AVXS at 1.1 X 10 ¹⁴ vg/kg	<u>Inclusion Criteria</u> Age ≤6 weeks at time of dose Compound muscle action potential (CMAP) Age ≤6 weeks (≤42 days) at time of dose Ability to tolerate thin liquids Patients with 2 copies of SMN2 (n ≥15) Patients with presymptomatic SMA Type I <u>Exclusion Criteria</u> Weight at screening visit <2 kg Hypoxemia Any clinical signs or symptoms at screening or immediately prior to dosing that are	<u>Primary Outcomes</u> 2 copies of SMN2 gene: functional independent sitting 3 copies of SMN2 gene: standing with support 4 copies of SMN2 gene: demonstrating motor improvements inconsistent with SMA natural history	April 2023

			Tracheostomy or current prophylactic use or requirement of noninvasive ventilatory support Treatment with an investigational or commercial product, including Spinraza, given for the treatment of SMA.		
Study of intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG) AveXis, Inc. NCT03381729	Phase I, non-randomized, parallel assignment, open-label Estimated enrollment:	<u>Intervention:</u> AVXS-101 <u>Experimental: Dose A</u> 6.0 x 10 ³ vg of avxs-101 <u>Experimental: Dose B</u> 1.2 x 10 ¹⁴ vg of avxs-101	<u>Inclusion Criteria:</u> Patients up to 60 months of age at time of dosing Diagnostic confirmation by genotype Negative gene testing for SMN2 gene modifier Onset of clinical signs + symptoms Able to sit independently and not standing or walking independently <u>Exclusion Criteria:</u> Current or historical ability to stand or walk independently Severe contractures as determined by designated physical therapist Severe scoliosis Previous, planned, or expected scoliosis procedure Use of invasive ventilatory support Medical necessity for feeding tube	<u>Primary Outcomes</u> Incidence of adverse events Determine optimal dose Patients <24 months: standing milestone Patients ≥24 months and <60 months: change in HFMSE score <u>Secondary Outcomes</u> Patients <24 months: walking milestone Patients ≥24 months and <60 months: walking milestone	September 1, 2020

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Spinraza					
A Study for Participants with Spinal Muscular Atrophy (SMA) Who Previously Participated in Spinraza Investigational Studies. (SHINE) Biogen <u>NCT02594124</u>	Phase III, non-randomized, parallel assessment, triple-masking (participant, investigator, outcomes assessor) Estimated Enrollment: 292	<u>Experimental Group 1:</u> Participants transitioned from ISIS 396443-CS3B (NCT02193074) <u>Intervention:</u> Spinraza <u>Experimental Group 2:</u> Participants transitioned from ISIS 396443-CS4 (NCT02292537) <u>Intervention:</u> Spinraza <u>Experimental Group 3:</u> Participants transitioned from ISIS 396443-CS12 (NCT02052791) <u>Intervention:</u> Spinraza <u>Experimental Group 4:</u> Participants transitioned from	<u>Inclusion Criteria</u> Signed informed consent Completion of index study <u>Exclusion Criteria</u> Have any condition or worsening condition that in investigator opinion would make the participant ineligible Clinically significant abnormalities in hematology Participant's guardian is not willing or able to meet standard of care guidelines Treatment with another investigational agent, biological agent, or device within a month of screening	<u>Primary Outcomes</u> Number of patients experiencing: AEs or SAEs clinically significant vital sign abnormalities weight abnormalities neurological abnormalities laboratory abnormalities coagulation abnormalities 12-lead electrocardiograms <u>Secondary Outcomes</u> Percentage of participants who Attained motor milestones Not required permeant ventilation Change from baseline in CHOP-INTEND motor function scale Change from baseline in Hammersmith Functional Motor Scale Change from baseline in revised upper limb module Change from baseline 6-minute walk test Change from baseline in body length, head/chest/arm circumference CMAP responders	August 1, 2023

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
		<p>ISIS 396443-CS3A (NCT01839656)</p> <p><u>Intervention:</u> Spinraza</p> <p><u>Experimental:</u> <u>Group 5:</u> Participants transitioned from 232SM202 (NCT02462759)</p> <p><u>Intervention:</u> Spinraza</p>			

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Multiple Doses of Spinraza (ISIS 396443) Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy Biogen <u>NCT02386553</u>	Phase II, single group assessment, open label Estimated enrollment: 25	<u>Intervention:</u> Spinraza administered as an intrathecal injection	<u>Inclusion Criteria</u> Age <6 weeks at first dose Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation Genetic documentation of 2 or 3 copies of SMN2 Ulnar compound muscle action potential <u>Exclusion Criteria</u> Hypoxemia Any clinical signs of SMA Clinically significant abnormalities Treatment with investigational drug given for the treatment of SMA biological agent or device	<u>Primary Outcomes</u> Time to death or respirator incident <u>Secondary Outcomes</u> Percentage of participants developing clinically manifested SMA who attained motor milestones assessed as part of the Hammersmith Infant Neurological Examination (HINE) who attained motor milestones as assessed by World Health Organization (WHO) criteria Change from Baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale Change from Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) Change from Baseline in weight for age/length Change from Baseline in arm/chest / head circumference ratio Incidence of adverse events (AEs) and/or serious adverse events (SAEs)	January 26, 2022

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Assess the Safety and Tolerability of Spinraza (ISIS 396443) in Participants with Spinal Muscular Atrophy (SMA) (EMBRACE) Biogen NCT02462759	Phase II, randomized, parallel assignment, quadruple masking Estimated enrollment:	<u>Intervention</u> Spinraza <u>Intervention</u> Sham comparator	<u>Inclusion Criteria:</u> Genetic documentation of 5q SMA homozygous gene deletion, mutation, or compound heterozygote Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures. <u>Exclusion Criteria:</u> Meets additional study criteria Any previous exposure to ISIS 396443 Clinically significant abnormalities to hematology	<u>Primary Outcomes</u> number of participants with adverse events and serious adverse events Change from Baseline in clinical laboratory parameters Change from Baseline in electrocardiograms (ECGs) Change from Baseline in vital signs Change from Baseline in neurological examination outcomes	April 9, 2019

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Spinraza in Adult Spinal Muscular Atrophy (SAS) Washington University School of Medicine <u>NCT03709784</u>	Longitudinal, observational study Estimated enrollment: 73	<u>Intervention</u> Spinraza	<u>Inclusion</u> Males and females with SMA type II or III, aged 18 to 60 years at the time of enrollment Genetic documentation of 5Q homozygous gene deletion, mutation, or compound heterozygote. Are treatment naïve to Spinraza Estimated life expectancy at least 30 months from first dosing Revised upper limb module (RULM) score ≥ 4 Group 1 Be free of major orthopedic deformities that limit ambulation Group 2 Ability to walk at least 10 meters without assistance Be free of major orthopedic deformities that limit ambulation An ambulatory subject can qualify for both group 1 and group 2 if the RULM score is ≤ 34 <u>Exclusion</u> revised upper limb score ≤ 3 Respiratory insufficiency Hospitalization/presence of severe symptoms Previous exposure to Spinraza	<u>Primary Outcomes</u> Change from baseline in the 6-minute walk test (6MWT) for ambulatory patients Change from baseline in Revised upper limb module (RULM) for weak ambulatory and non-ambulatory SMA patients	January 30, 2022

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
European Registry of Patients with Infantile-onset Spinal Muscular Atrophy Institut de Myologie, France NCT03339830	Observational (patient registry)	Any	<u>Inclusion</u> Spinal Muscular Atrophy diagnosed in childhood and genetically confirmed For patients with SMA type I: never acquired independent sitting position (more than 30 sec. without hand support or any external support) For any patients with SMA type II or III: patients treated with a market approved treatment for SMA or with a treatment in an expanded access program Any age Patients over 18 years of age or parent(s)/legal guardian(s) of patients <18 years of age not opposed to data collection for research purposes	<u>Primary Outcomes</u> Change from baseline to survival in psychomotor development number in lower track infections ventilation use cough assist use forced vital capacity diurnal saturation nocturnal hypercapnia <u>Secondary Outcomes</u> Change from baseline in treatment of psychomotor development in the number of hospitalizations in duration of hospitalizations in scoliosis occurrence in arthrodesis occurrence in wheelchair use in feeding status in HINE-2 in CHOP-INTEND score In HFMSE In therapy sessions per week	December 1, 2022

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness

Supplemental Information

Study Selection and Quality Assessment

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to Spinraza. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table D1).⁷¹ Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking*

outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

A study quality rating was not assigned to grey literature (conference abstracts/posters) because they lack granular details. Additionally, we did not rate the quality of non-comparative studies (NURTURE , CS3A, CS2/CS12, CL-101) or OLEs (SHINE).

Table D1. Study Quality Assessment Results

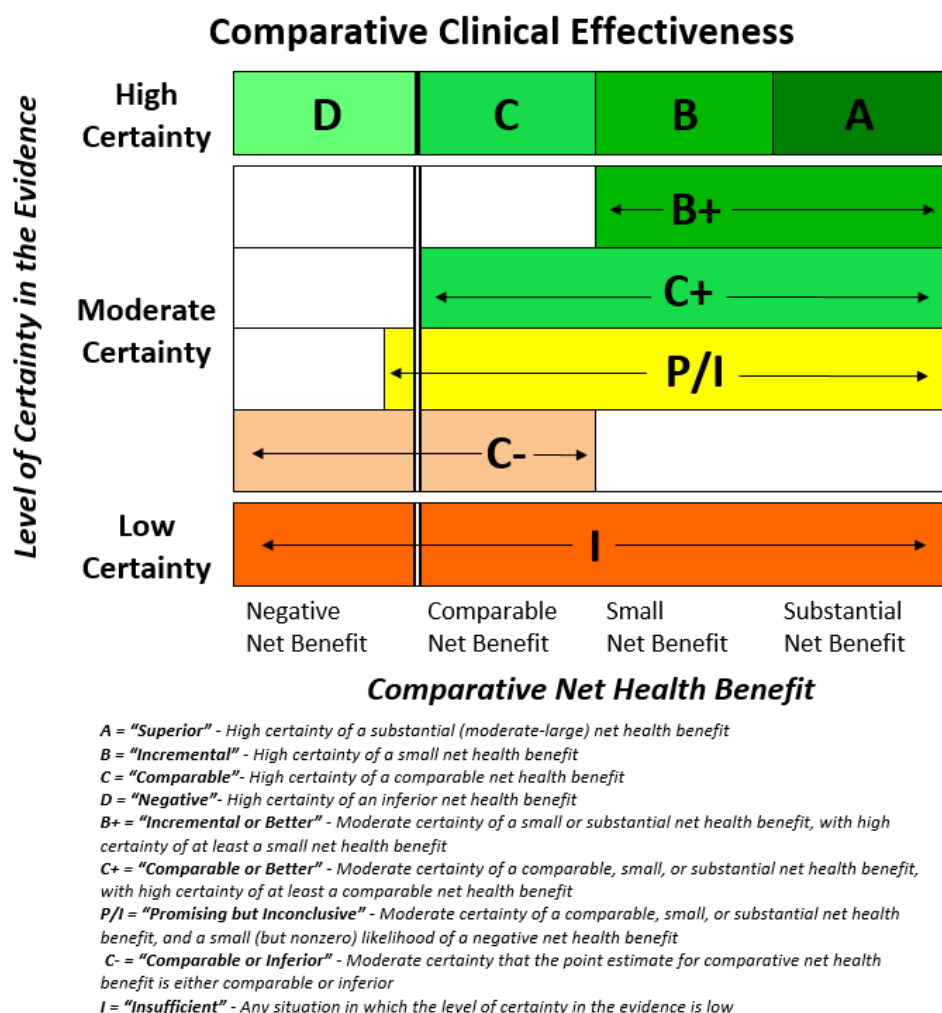
Study	Comparable Groups	Double-Blind	Measurements Equal and Valid	Clear Definition of Intervention	Key Outcomes Assessed	Quality
ENDEAR	Yes	Yes	Yes	Yes	Yes	Good
CHERISH	Yes	Yes	Yes	Yes	Yes	Good
EMBRACE	Yes	Yes	Yes	Yes	Yes	Good

ICER Evidence Rating

We used the [ICER Evidence Rating Matrix](#) (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

- The **magnitude** of the difference between a therapeutic agent and its comparator in “net health benefit” – the balance between clinical benefits and risks and/or adverse effects AND
- The level of **certainty** in the best point estimate of net health benefit.⁷²

Figure D1. ICER Evidence Rating Matrix



Supplemental Data

Table D2. Baseline Study Characteristics

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Type I										
ENDEAR										
Finkel, 2017 ¹⁷	Randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial	13 months	Spinraza	80	163 (range: 52–242) days	7.9 (2–18) weeks	12.6 (0 - 29) weeks	13.2 (0–25.9) weeks	43 (54)	NR
			Sham control	41	181 (range: 30–262) days	9.6 (2–30) weeks	17.5 (2 - 30) weeks	13.9 (0–23.1) weeks	24 (59)	NR
Servais, 2017 ⁷⁶	Subgroup analysis by median disease duration (≤12 vs. >12 weeks); final analysis set	13 months	DD ≤12 weeks; sham	18	136.0 (30–228) days	8.0 (1–20) weeks	10.5 (2–25) weeks	9.9 (0–12) weeks	7 (39)	NR
			DD ≤12 weeks; Spinraza	34	117.0 (52–235) days	6.0 (3–18) weeks	9.5 (0–22) weeks	8.7 (0–12) weeks	18 (53)	NR
			DD >12 weeks; sham	23	213.0 (143–262) days	8.0 (4–16) weeks	20.0 (12–30) weeks	18.0 (13–23) weeks	17 (74)	NR
			DD >12 weeks; Spinraza	46	196.0 (127–242) days	8.0 (2–16) weeks	12.0 (2–29) weeks	16.3 (12–26) weeks	25 (54)	NR
McNeil, 2017 ¹⁰⁰	Phase 3, randomized, double-blind,	13 months	≤13 weeks: Spinraza	39	NR	NR	NR	NR	NR	NR
			≤13 weeks: control	21	NR	NR	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
	sham controlled procedure		≥13 weeks: Spinraza	41	NR	NR	NR	NR	NR	NR
			≥13 weeks: control	20	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018 ²⁶	Open-label extension study	Up to 5 years	Spinraza → Spinraza	81	5.4 (2–15) months	1.6 (0–4) months	NR	NR	NR	NR
			Sham → Spinraza	24	17.8 (10–23) months; age at first dose	Median: 2.1 (1–5) months	NR	NR	NR	NR
CS3A / Phase II										
Darras, 2013 ¹⁰¹	Open-label, dose-escalating	88 days	1, 3, 6 or 9 mg of Spinraza	28	2-14 years	NR	NR	NR	NR	NR
Finkel, 2016 ¹⁶	Phase 2, open-label, dose-escalating study	32 months	6-12 mg	4	145 (67-207) days	47 (28–70) days	74 (42-105) days	NR	1 (25)	7.1 (5.2-8.9) kg
			12 mg	16	140 (36-210) days	63 (21-154) days	80 (0-154) days	NR	7 (44)	6.7 (5.1-9.3) kg
EMBRACE										
Shieh, 2018 ³⁶	Phase 2, double-blind, sham-controlled	14 months	≥6 months (12 mg Spinraza)	5	18.1 (16-19) months	9.0 (7.6-11.0) months	13.0 (9.9-15.0) months	NR	1 (20)	NR
			≥6 months (sham)	3	17.0 (15-19) months	9.0 (7.0-11.0) months	13.0 (12.0-14.0) months	NR	2 (67)	NR
			≤6 months (12 mg Spinraza)	9	15.3 (7-79) months	4.6 (2.0-6.0) months	8.0 (6.9-11.0) months	NR	4 (44)	NR
			≤6 months (sham)	4	25.6 (16-53) months	3.85 (1.8-5.1) months	7.7 (5.5-14.0) months	NR	3 (75)	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Expanded Access Program (EAP)										
Farrar, 2018 ⁷⁵	Prospective, multicenter study (Australia)	NR	New SMA diagnosis during Spinraza EAP	8	NR	2.8 (1-5) weeks	6.4 (2.1-11) (NR)	5.0 (0.5-72) months	3 (NR)	NR
			SMA diagnosis prior to EAP start	8	NR	5.1 (3-5.9) weeks	10.5 (7-72) (NR)	5.0 (0.5-72) months	5 (NR)	NR
Scoto, 2018 ¹⁰²	Observational	9 months	Spinraza	69	14 (1-9.5)	NR	NR	NR	39 (65)	NR
Pechmann, 2018 ⁷³	Prospective, multicenter study (Germany)	6 months	Spinraza	61	21.1 (1-93)	2.78 (0-6) months	N/A	NR	30 (49)	NR
Pane, 2018 ⁷⁴	Prospective, multicenter study (Italy)	6 months	Spinraza	104	3-19 (months to years)	NR	NR	NR	NR	NR
CL-101 (Zolgensma)										
Mendell, 2017 ²²	Phase 1, single-arm, open-label	24 months	Low dose	3	6.3 (5.9-7.2) months	1.7 (1.0-3.0) months	33 (4-85) days	NR	2 (67)	6.6 (6.0-7.1)
			High Dose	12	3.4 (0.9-7.9) months	1.4 (0-3.0) months	60 (0-136) days	NR	7 (58)	5.7 (3.6-8.4)
Al-Zaidy, 2019 ³²	Phase 1, single-arm, open-label	24 months	High Dose	12	3.4 (0.9 – 7.9)	NR	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Types II and III										
CHERISH										
Mercuri, 2018 ¹⁸	Multicenter, double-blind, sham-controlled, phase 3 trial	15 months	Spinraza	84	4.0 (NR)	10 (6-20) weeks	18 (0-40) months	39.3 (8-94) months	46 (55)	NR
			Sham control	42	3.0 (NR)	11 (6 - 20) weeks	18 (0 - 46) months	30.2 (10-80) months	21 (50)	NR
Mercuri, 2017 ¹⁰³	Phase 3, randomized, double-blind sham controlled	15 months	Spinraza	35	NR	NR	NR	NR	NR	NR
			Sham control	19	NR	NR	NR	NR	NR	NR
Stolte, 2018 ⁷⁷	Open-label , single-arm study	NR	Spinraza, Type II	9	31.2 (24-48) years	NR	NR	NR	6 (66.7)	NR
			Spinraza, Type III	19	37.9 (18-61) years	NR	NR	NR	4 (21.1)	NR
Wurster , 2018 ⁷⁸	Open-label , single-arm study	NR	Spinraza, Type II	9	27.0 (11-48)	NR	NR	NR	NR	NR
			Spinraza, Type III	11	37.6 (13-60)	NR	NR	NR	NR	NR
CS2, CS12										
Chiriboga, 2017 ²⁸	Multicenter, open-label study	1050 days	SMA type II	11	4.4 (4.0) years	11.0 (3.4) months	15.4 (6.3) months	NR	3 (27)	NR
			SMA type III	17	8.9 (4.4) years	22.0 (13.5) months	43. 6 (32.4) months	NR	10 (59)	NR
Montes et al, 2018 ¹⁰⁴	Multi-center, open-label clinical trial	1050 days	Spinraza (multiple doses)	14	8.6 years (age at screening)	23.9 (NR) months	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
STRIVE										
Day, 2018 ¹⁰⁵	Open-label, multicenter, phase 3	baseline data update	Spinraza	22	3.7 (0.5-5.9) months	1.9 (0-4.0) weeks	62 (15-120) days	NR	12 (55)	5.8 (3.9-7.5) kg
NURTURE (Presymptomatic)										
De Vivo, 2017 ¹⁰⁶	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	9	NR	NR	NR	NR	NR	NR
De Vivo, 2018 ¹⁰⁷ (Cure SMA)	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	25	See Swoboda 2018 for baseline	NR	NR	NR	NR	NR
Swoboda, 2018 ³⁷	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	25	Median at age of first dose: 22.0 (3-42) days	N/A	N/A	N/A	13 (52)	NR

DD: disease duration, MDD: median disease duration, N/A: not applicable, NR: not reported

Table D3. Baseline Motor Milestones

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
ENDEAR (Type I)										
Finkel, 2017 ¹⁷	Interim and final (max 13 months)	Spinraza	80	NR	1.29 ± 1.07 (SD)	26.63 ± 8.13	21 (26)	7 (9)	NR	NR
		Sham control	41	NR	1.54 ± 1.29 (SD)	28.43 ± 7.56	6 (15)	5 (12)	NR	NR
Servais, 2017 ⁷⁶	Subgroup analysis by median disease duration (≤12 vs. >12 weeks); final analysis set	DD ≤12 weeks; sham	18	N/A	NR	NR	2 (11)	NR	NR	NR
		DD ≤12 weeks; Spinraza	34	N/A	NR	NR	4 (12)	NR	NR	NR
		DD >12 weeks; sham	23	N/A	NR	NR	4 (17)	NR	NR	NR
		DD >12 weeks; Spinraza	46	N/A	NR	NR	17 (37)	NR	NR	NR
McNeil, 2017 ¹⁰⁰	13 months	DD ≥13 weeks: Spinraza	39	NR	NR	NR	NR	NR	NR	NR
		DD ≥13 weeks: control	21	NR	NR	NR	NR	NR	NR	NR
		DD ≤13 weeks: Spinraza	41	NR	NR	NR	NR	NR	NR	NR
		DD ≤13 weeks: control	20	NR	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018 ²⁶	Interim	Spinraza → Spinraza	81	NR	1.3 (1.08)	26.7 (8.13)	NR	NR	NR	NR
		Sham → Spinraza	24	NR	1.3 (1.08)	17.3 (9.71)	NR	NR	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
CS3A/ Phase 2										
Darras, 2013 ¹⁰¹	NR	1, 3, 6, or 9 mg of Spinraza	28	NR	NR	NR	NR	NR	NR	NR
Finkel, 2016 ¹⁶	32 months	6-12 mg	4	NR	2 (1-3)	27 (22-34)	0	1	NR	NR
		12 mg	16	NR	2 (1-12)	30 (17-64)	0	1	NR	NR
EMBRACE										
Shieh, 2018 ³⁶	14 months	≥6 months (12mg Spinraza)	5	NR	NR	NR	NR	NR	NR	NR
		≥6 months (sham)	3	NR	NR	NR	NR	NR	NR	NR
		≤6 months (12 mg NSRSN)	9	NR	NR	NR	NR	NR	NR	NR
		≤6 months (sham control)	4	NR	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)										
Farrar, 2018 ⁷⁵	NR	New SMA diagnosis during Spinraza EAP	8	NR	NR	NR	NR	NR	NR	NR
		SMA diagnosis prior to EAP start	8	NR	NR	NR	NR	NR	NR	NR
Scoto, 2018 ¹⁰²	9 months	Spinraza	69	NR	NR	25/64 (5-52)	36/69 required NIV	1 (needed a tracheostomy)	NR	NR
Pechmann, 2018 ⁷³	6 months	Spinraza	61	N/A	0.8 (range: 0-8)	22.3 (range: 1-50)	18 (29.5); NIV >16 h/day + tracheostomy categories	34 (55.7); "Feeding tube or gastronomy"	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
Pane, 2018 ⁷⁴	6 months	Spinraza	104	NR	NR	15.08 (13.53)	NR	NR	NR	NR
CL-101 (Zolgensma)										
Mendell, 2017 ²²	24 months	Low dose	3	NR	NR	16 (6-27)	3 (100)	3 (100)	NR	NR
		High Dose	12	NR	NR	28.2 (12-50)	2 (17)	5 (42); 4 (33) ability to swallow	NR	NR
Al-Zaidy, 2019 ³²	24 months	High Dose	12	NR	NR	NR	83 (did NOT require ventilation)	NR	NR	NR
Types II and III										
CHERISH										
Mercuri, 2018 ¹⁸	15 months (9 months of treatment + 6 months of follow up)	Spinraza	84	22.4 ± 8.3; scores	NR	NR	NR	NR	1.4 ± 1.0	19.4 ± 6.2
		Sham control	42	19.9 ± 7.2	NR	NR	NR	NR	1.5 ± 1.0	18.4 ± 5.7
Mercuri, 2017 ¹⁰³	Interim	Spinraza	35	NR	NR	NR	NR	NR	NR	NR
		Sham control	19	NR	NR	NR	NR	NR	NR	NR
Stolte, 2018 ⁷⁷	NR	Spinraza, Type II	9	3.1 ± 2.5	NR	NR	NR	NR	NR	9.9 ± 4.6
		Spinraza, Type III	19	31.2 ± 18.1	NR	NR	NR	NR	NR	29.5 ± 8.5
Wurster, 2018 ⁷⁸	NR	Spinraza, Type II	9	1.7 (2.2)	NR	NR	7/9 use NIV	2/9 use PEG	NR	NR
		Spinraza, Type III	11	30.1 (25.0)	NR	NR	0/11 use NIV	0/11 use PEG	NR	NR
CS2, CS12										
Chiriboga, 2017 ²⁸	1050 days	SMA Type II	11	21.3 (SE: 2.9)	NR	NR	NR	NR	NR	NR
		SMA Type III	17	48.9 (SE: 3.0)	NR	NR	NR	NR	NR	NR
Montes et al, 2018 ¹⁰⁴	1050 days	Spinraza	14	NR	NR	NR	NR	NR	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
STRIVE OLE (Type I)										
Day, 2018 ¹⁰⁵	baseline data update	Spinraza	22	NR	NR	32 (17-52)	0 (0)	0 (0)	NR	NR
NURTURE (Presymptomatic)										
De Vivo, 2017 ¹⁰⁶	1 year (interim results)	Spinraza (12 mg)	9	NR	NR	NR	NR	NR	NR	NR
De Vivo, 2018 (Cure SMA) ¹⁰⁷	Interim	Spinraza (12 mg)	25	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018 ³⁷	Interim	Spinraza (12 mg)	25	N/A	3.0 (0-7); Total milestones	50.0 (25.0-60.0)	NR	NR	NR	NR

DD: disease duration, EAP: expanded access program, MDD: moderate disease duration, N/A: not applicable, NIV: non-invasive ventilation, NR: not reported

Table D4. Outcomes I: Survival, Event-Free Survival

					Survival			Event Free Survival			
	Timepoint	Arm	Treatment N	Placebo N	No. Alive in Treatment Arm	No. Alive in Placebo Arm	Treatment Difference?	Definition	Estimate for Treatment Arm	Estimate for Placebo Arm	Treatment Difference
ENDEAR (Type I)											
Finkel, 2017 ¹⁷	Final analysis	--	80	41	67 (84)	25 (61)	HR (95% CI): 0.37 (0.18-0.77)	NR	Not reached	22.6 weeks	HR (95% CI): 0.53 (0.32-0.89)
Servais, 2017 ⁷⁶	Final analysis set	≤12 weeks	34	18	NR	NR	HR, 0.219; P=.0299	NR	NR	NR	HR: 0.158 (p=0.004, no 95% CI)
		>12 weeks	46	23	NR	NR	HR, 0.455; P=.0880	NR	NR	NR	HR: 0.816 (p=0.5325, no 95% CI)
McNeil , 2018 ¹⁰⁰	Final analysis set	≤13.1 weeks	39	21	NR	NR	NR	Time to death or permanent ventilation	9 (11%)	14 (34)	NR
		>13.1 weeks	41	20	NR	NR	NR		22 (28%)	14 (34)	NR
SHINE (OLE)											
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza : 24	NR	NR	NR	Time to death or permanent ventilation	22.6 (13.6 -31.3)	73.0 (36.3 – N/A)	NR
CS3A/ Phase 2											
Finkel, 2016 ¹⁶	32 months	--	4	16	NR	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)											
Scoto, 2018 ¹⁰²	9 months	--	69	NA	65	NA	NR	NR	NR	NR	NR

					Survival			Event Free Survival			
	Timepoint	Arm	Treatment N	Placebo N	No. Alive in Treatment Arm	No. Alive in Placebo Arm	Treatment Difference?	Definition	Estimate for Treatment Arm	Estimate for Placebo Arm	Treatment Difference
Pechmann, 2018 ⁷³	24 months	--	61	N/A	60	N/A	N/A	NR	NR	NR	NR
CL-101 (Zolgensma)											
Mendell, 2017 ²²	24 months	Low dose	3	N/A	3	N/A	N/A	NR	NR	NR	N/A
		High dose	12	N/A	12	N/A	N/A	NR	NR	NR	N/A
Al-Zaidy, 2019 ³²	38 months	High dose	12	N/A	12	N/A	NR	Alive and without permanent ventilation	100% - 1 patient needs ventilation needs are below 16 hrs./day	N/A	NR
CHERISH (Type II, II)											
Mercuri, 2018 ¹⁸	Final analysis	--	84	42	84	42	Median: 4.0 (2-9)	NR	NR	18 (0-48) months	N/A
NURTURE (Presymptomatic)											
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	2 copies SMN2	6	0	6	N/A	N/A	All alive without permanent ventilation	N/A	N/A	N/A
		3 copies SMN2	3	0	3	N/A	N/A		N/A	N/A	N/A
Swoboda, 2018 ³⁷	Interim	--	25	N/A	25 (100%)	N/A	N/A	NR	NR	N/A	N/A

N/A: not applicable, NR: not reported

Table D5. Outcomes II: Ventilation

	Timepoint	Arms	Treatment N	Placebo N	Definition	No. People Not Ventilated in Treatment Arm	No. People Not Ventilated in Placebo	Treatment Difference
ENDEAR (Type I)								
Finkel, 2017 ¹⁷	Final analysis	--	80	41	Tracheostomy or ventilatory support for at least 16 hours per day for more	62 (78)	28 (68)	HR (95% CI): 0.66 (0.32-1.37)
Servais, 2017 ⁷⁶	Final Analysis	≤12 weeks	34	18	NR	NR	NR	NR
		≥12 weeks	46	23	NR	NR	NR	NR
McNeil , 2018 ¹⁰⁰	13 months	≤13 weeks:	39	21	NR	NR	NR	NR
		≥13 weeks:	41	20	NR	NR	NR	NR
SHINE (OLE)								
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	NR	NR	NR	NR
CS3A/ Phase 2								
Finkel, 2016 ¹⁶	32 months	--	4	16	21 continuous days in the absence of an acute reversible event	NR	NR	p=0.0014
Expanded Access Program (EAP)								
Scoto, 2018 ¹⁰²	9 months	--	69	N/A	Additional patients who needed ventilation	7	NR	43 (total)
Pechmann, 2018 ⁷³	NR	--	61	N/A	Non-invasive ventilator >16 hr/day + tracheostomy	19	N/A	N/A
CL-101 (Zolgensma)								
Mendell, 2017 ²²	24 months	Low dose	3	N/A	≥16 hours/day of continuous respiratory support for at least 14 days in the absence of an acute, reversible illness or perioperative state	1	N/A	N/A
		High dose	12	N/A		12 (100%)	N/A	N/A
Al-Zaidy, 2019 ³²	38 months	high dose cohort	12	N/A	Of 10 patients who did not require BiPAP support before	7 (70%)	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	Definition	No. People Not Ventilated in Treatment Arm	No. People Not Ventilated in Placebo	Treatment Difference
					dosing, # of patients who continued to not require BiPAP 24 months after dosing			
CHERISH (Type II, III)								
Mercuri, 2018 ¹⁸	Final analysis	--	84	42	NR	NR	10 (6-20) months	NR
NURTURE (Presymptomatic)								
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	2 copies SMN2	6	0	Tracheostomy/ventilation for ≥6 hours/day for ≥7 days	6	N/A	N/A
		3 copies SMN2	3	0		3	N/A	N/A
Swoboda, 2018 ³⁷	Interim	--	25	N/A	≥16 hour/day continuously for >21 days (permanent ventilation) in the absence of an acute, reversible event or tracheostomy	0	N/A	N/A

DD: disease duration, MDD: moderate disease duration, N/A: not applicable, NIV: non-invasive ventilation, NR: not reported

Table D6. Outcomes III: CHOP-INTEND

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
ENDEAR (Type I)										
Finkel, 2017 ¹⁷	Final analysis	--	80	41	52 / 73 (71%)	1 / 37 (3%)	P = <0.0001	NR	NR	NR
Servais, 2017 ⁷⁶	Final analysis	≤12 weeks	34	18	88% (of 32)	0	NR	NR	NR	NR
		>12 weeks	46	23	59% (of 16)	5% (of 21)	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	51	4	NR	NR	16.9 (11.9–21.9)	3.6 (–0.9 to 8.1)
CS3A / Phase 2										
Finkel, 2016 ¹⁶	32 months	--	4	16	14	12	11.5	15.2	p = 0.0080	p = 0.0013
EMBRACE										
Shieh, 2018 ³⁶	14 months	Onset ≤6 month	9	4	NR	NR	NR	NR	NR	NR
		Onset >6 month	5	3	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)										
Scoto, 2018 ¹⁰²	9 months	--	69	NA	1-17 points	NR	36/64	NR	NR	NR
Pechmann, 2018 ⁷³	NR	--	61	N/A	47 (77.0%)	N/A	31.2 ± 16.2 (SD)	N/A	9.0 ± 8.0 (SD)	N/A
Pane, 2018 ⁷⁴	6 months	--	104	NA	-7 to 27	NR	4.51 (5.80)	NR	P < 0.001	NR

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
CL-101 (Zolgensma)										
Mendell, 2017 ²²	24 months	Low dose	3	N/A	NR	N/A	NR	NR	7.7 (from baseline)	N/A
		proposed therapeutic dose	12	N/A	22.5 (mean increase)	N/A	NR	NR	9.8 (month 1); 15.4 (month 3); 24.6 (at study cutoff)	N/A
NURTURE (Presymptomatic)										
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	2 copies SMN2	6	0	N/A	N/A	All pts: 62.0 (44-64)	N/A	N/A	N/A
		3 copies SMN2	3	0	N/A	N/A	All pts: 62.0 (44-64)	N/A	N/A	N/A
Swoboda, 2018 ³⁷	Interim	--	25	N/A	NR	N/A	NR	N/A	NR	N/A

N/A: not applicable, NR: not reported

Table D7. Outcomes IV: Sitting, Walking, Standing

Study					Sitting		Standing		Walking	
	Timepoint	Arms	Treatment N	Placebo N	No. (%) of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo
ENDEAR (Type I)										
Finkel, 2017 ¹⁷	Final analysis	--	80	41	8%	0	1%	0	NR	NR
Servais, 2017 ⁷⁶	Final analysis	≤12 weeks	34	18	NR	NR	NR	NR	NR	NR
		≥12 weeks	46	23	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza : 24	Day 64: NR (1%) of 70; Day 183 5% of 65; Day 302: 10% of 51; Day 394: 15% of 48; Day 578: 29% of 31; Day 698: 24% of 17	NR	0	0	0	0
CS3A/ Phase 2										
Finkel, 2016 ¹⁶	32 months	--	4	16	NR	NR	NR	NR	NR	NR
EMBRACE										
Shieh, 2018 ³⁶	14 months -	Onset ≤6 month	9	4	5 (56)	0	0	0	0	0
		Onset >6 month	5	3	4 (80)	1 (33)	2 (40)	2 (67)	1 (20)	0
Expanded Access Program (EAP)										
Pechmann, 2018 ⁷³	NR	--	61	N/A	2 (3.3%)	N/A	0	N/A	0	N/A
CL-101 (Zolgensma)										
Mendell, 2017 ²²	24 months	Low dose	3	N/A	NR	N/A	NR	N/A	NR	N/A
		High dose	12	N/A	75% (rolls over); 92% (sits with	N/A	2	N/A	2	N/A

Study					Sitting		Standing		Walking	
	Timepoint	Arms	Treatment N	Placebo N	No. (%) of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo
					assistance); 92% sits unassisted ≥5 sec; 83% sits unassisted ≥10 sec; 75% sits unassisted ≥30 sec					
Al-Zaidy, 2019 ³²	38 months	High Dose	12	N/A	92% (sitting with assistance) ; 92% (sitting unassisted > 5s) ; 92% (sitting unassisted > 10s) ; 92% (sitting unassisted > 30s)	N/A	33% (standing assisted)	N/A	NR	N/A
CHERISH (Types II, III)										
Mercuri, 2018 ¹⁸	Final analysis	--	84	42	NR	22.4 ± 8.3 (SD)	1(2)	1 (3)	1 (2)	0 (0)
NURTURE (Presymptomatic)										
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	2 copies SMN2	6	0	3 (50) pivots	N/A	1 (17) stands unaided	N/A	2 (33) cruising	N/A
		3 copies SMN2	3	0	3 (100) pivots	N/A	2 (67) stands unaided	N/A	3 (100) cruising	N/A
Swoboda, 2018 ³⁷	Interim	--	25	N/A	25 (100)	N/A	NR	N/A	22 (88)/17 (77)	N/A

N/A: not applicable, NR: not reported

Table D8. Outcomes V: HFMSE

	Timepoint	Arm	Treat ment N	Placebo N	Definition of Response	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
Phase 2											
Darras, 2013 ¹⁰¹	3 months	--	1 or 3 mg	6 or 9 mg	NR	NR	6/10	NR	3.1	NR	NR
Type II and III											
CHERISH											
Mercuri, 2018 ¹⁸	Interim	--	35	19	HFMSE score ≥3 points	NR	NR	NR	NR	4.0 (2.9, 5.1)	-1.9 (-3.8, 0)
Mercuri, 2018 ¹⁸	Final analysis	--	66	34	--	57 (46, 68)	26 (12, 40)	NR	NR	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)
Wurster, 2018 ⁷⁸	After 4 loading doses, per label schedule	Spinraza, Type II	9	0	N/A	N/A	N/A	2.0 (2.5)	N/A		N/A
		Spinraza, Type III	11	0	N/A	N/A	N/A	30.8 (24.8)	N/A		N/A
CS2, CS12											
Chiribog a, 2017 ²⁸	253 days	--	Type II - 11	0	HFMSE score ≥3 points	9/11 (82)	NR	NR	NR	NR	NR
	1050 days	--	Type II - 11	0		6/6 (100)	NR	NR	NR	12.3 (SE: 2.2)	NR
	253 days	--	Type III - 17	0		3/16 (19)	N/A	NR	NR	NR	NR
	1050 days	--	Type III - 17	0		2/7 (29)	N/A	NR	NR	1.6 (SE: 1.5)	NR

N/A: not applicable, NR: not reported

Table D9. Outcomes VI: HINE-2

Study	Timepoint	Arms	Treatment N	Placebo N	Definition of Responder	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)
ENDEAR (Type I)									
Finkel, 2017 ¹⁷	Interim analysis	--	80	41	improvement in at least one category AND more categories with improvement than categories with worsening	21/51 (41)	0/27	NR	NR
	Final analysis	--	80	41		37/73 (51)	0/37	NR	NR
Servais, 2017 ⁷⁶	Final analysis	≤12 weeks	34	18	(1) ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking or a ≥2-point increase or achievement of maximal score in kicking ability; and (2) improvement in more HINE categories than worsening.	75% (of 32)	0	P<0.0001	NR
		>12 weeks	46	23		32% (of 41)	0	P=0.0026	NR
SHINE (OLE)									
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → nusinersen: 24	≥2-point increase or achievement of touching toes in ability to kick, or ≥1-point increase in other 6	20/24	74/81	5.8 (4.58-7.04);	1.1 (0.20-1.90)
CS3A/ Phase 2									
Finkel, 2016 ¹⁶	32 months	--	4	16	improvement in at least one category	16	15	p=0.002	p=0.001
EMBRACE									
Shieh, 2018 ³⁶	14 months	Onset ≤6 month	9	4	Individuals demonstrating improvement in more motor milestone categories than worsening	7 (78)	0	0.78 (0.45-0.94)	0.80 (0.38-0.96)

Study	Timepoint	Arms	Treatment N	Placebo N	Definition of Responder	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)
		Onset ≥6 month	5	3		4 (80)	2 (67)	0 (0.00-0.60)	0.67 (0.21-0.94)
Expanded Access Program (EAP)									
Pechmann, 2018 ⁷³	NR	--	61	N/A	improvement in at least 1 category by ≥1 point and more categories with improvement than categories with worsening	21 (34.4%)	N/A	2.5 ± 3.3 (SD)	N/A
CS2, CS12									
Montes et al, 2018 ¹⁰⁴	253 days	--	14	0	NR	NR	N/A	NR	N/A
	1050 days	--	14	0	NR	NR	N/A	NR	N/A
Chiriboga, 2017 ²⁸	253 days	--	Type II - 11	0	NR	NR	NR	NR	NR
	1050 days	--	Type II - 11	0	NR	NR	NR	NR	NR
	253 days	--	Type III - 17	0	NR	NR	NR	NR	NR
	1050 days	--	Type III - 17	0	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Table D10. Outcomes VII: 6MWT

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
ENDEAR (Type I)								
Finkel, 2017 ¹⁷	Final analysis	--	80	41	NR	NR	NR	NR
Servais, 2017 ⁷⁶	≤12 weeks	End of study results	34	18	NR	NR	NR	NR
	≥12 weeks		46	23	NR	NR	NR	NR
SHINE (OLE)								
Castro, 2018 ²⁶	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	N/A	N/A	N/A	N/A
CS3A/ Phase 2								
Finkel, 2016 ¹⁶	32 months	--	4	16	NR	NR	NR	NR
EMBRACE								
Shieh, 2018 ³⁶	14 months	Onset ≤6 month	9	4	NR	NR	NR	NR
		Onset >6 month	5	3	NR	NR	NR	NR
Expanded Access Program (EAP)								
Pechmann, 2018 ⁷³	NR	--	61	N/A	NR	NR	NR	NR
CS2, CS12								
Montes et al, 2018 ¹⁰⁴	253 days	--	14	0	NR	N/A	17 (-47, 99)	N/A
	1050 days	--	14	0	NR	N/A	99.0 (31, 150)	N/A
Chiriboga, 2017 ²⁸	253 days	--	Type II - 11	0	N/A	N/A	N/A	N/A
	1050 days	--	Type II - 11	0	N/A	N/A	N/A	N/A
	253 days	--	Type III - 17	0	6/12 (50)	N/A	NR	N/A
	1050 days	--	Type III - 17	0	6/6 (100)	N/A	96.7 (17.3)	N/A

N/A: not applicable, NR: not reported

Table D11. Outcomes VIII: Other

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
ENDEAR (Type I)												
Finkel, 2017 ¹⁷	6 months, early termination	<13.1 weeks	80	41	22% Full head control	0	30/39 (77)	7/21 (33)	NR	NR	NR	NR
		>13.1 weeks					19/41 (46)	6/20 (30)	NR	NR	NR	NR
SHINE (OLE)												
Castro, 2018 ²⁶	Interim analysis	--	Nusinersen → Spinraza: 81	Sham → Spinraza: 24	Full head control: Day 64: 7% of 70; Day 183: 17% of 65; Day 302: 25% of 51; Day 394: 33% of 48; Day 578: 45% of 31; Day 698: 35% of 17	NR	NR	NR	NR	NR	N/A	N/A
Swoboda, 2018 ³⁷	Interim	--	25	N/A	88% (of 25); "Good suck and swallow"	N/A	NR	NR	NR	NR	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
EMBRACE												
Shieh, 2018 ³⁶	14 months	Onset ≤6 month	9	4	4 (44) Head control, ≥1-point increase	0	1.236 (3.712)	2.123 (3.023)	NR	NR	NR	NR
		Onset ≥6 month	5	3	1 (20) Head control, ≥1-point increase	0	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)												
Pechmann, 2018 ⁷³	NR	--	61	N/A	4 (6.6%) Head control; 37 (60.7%) GI tube	N/A	NR	NR	NR	NR	NR	NR
CL-101 (Zolgensma)												
Mendell, 2017 ²²	24 months	High dose	12	N/A	11 (swallow); 11 (speaking); 50% (GI tube)	N/A	5/12 had no support	NR	NR	NR	NR	NR
Al-Zaidy, 2019 ³²	38 months	High dose	12	N/A	11/12 (92%) swallow; 11/12 (92%) speaking	N/A	NR	N/A	NR	N/A	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
CHERISH (Types II, III)												
Mercuri, 2017 ¹⁰³	INTERIM	--	35	19	NR	NR	NR	NR	17.1%	10.5%	NR	Treatment difference: 3.4 (NR)
CS2, CS12												
Chiriboga, 2017 ²⁸	253 days	Type II	11	0	NR	NR	NR	NR	NR	NR	5/11 improved by ≥ 2 points	N/A
	1050 days		11	0	NR	NR	NR	NR	NR	NR	CFB: 4.6 (SE: 1.4); 4/6 improved by ≥ 2 points	N/A
	253 days	Type III	17	0	NR	NR	NR	NR	NR	NR	NR	N/A
	1050 days		17	0	NR	NR	NR	NR	NR	NR	NR	N/A

N/A: not applicable, NR: not reported

Table D12. Harms I (AEs, SAEs, Discontinuation, Death)

Study				Adverse Events		Serious Adverse Events (SAE)		Treatment-Related AE		AE Leading to Discontinuation		Deaths	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017 ¹⁷	Final analysis	80	41	77 (96)	40 (98)	61 (76)	39 (95)	NR	NR	13 (16)	16 (39)	NR	NR
SHINE (OLE)													
Castro, 2018 ²⁶	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraza, SHINE time only)	60 (92)	23 (96)	39 (60)	13 (54)	0	0	4 (6)	2 (8)	NR	NR
CS3A / Phase 2													
Finkel, 2016 ¹⁶	32 months	4	16	4 (100)	16 (100)	3 (75)	13 (81)	NR	NR	NR	NR	1	2
EMBRACE													
Shieh, 2018 ³⁶	14 months	14	7	14 (100)	6 (86)	5 (36)	3 (43)	0	0	0	0	0	1 (14)
Expanded Access Program (EAP)													
Pechmann, 2018 ⁷³	6 months	61	N/A	53	NR	29 (54.7%)	NR	NR	NR	NR	NR	1	NR
CL-101 (Zolgensma)													
Mendell, 2017 ²²	24 months - low dose	3	N/A	3 (100)	N/A	3 (100)	N/A	1 (33)	N/A	0	N/A	0	N/A
	24 months - proposed	12	N/A	12 (100)	N/A	10 (83)	N/A	3 (25)	N/A	0	N/A	0	N/A

Study				Adverse Events		Serious Adverse Events (SAE)		Treatment-Related AE		AE Leading to Discontinuation		Deaths	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
	therapeutic dose												
Types II and III													
Mercuri, 2018 ¹⁸	Final analysis	84	42	78 (93)	42 (100)	4 (5)	3 (7)	NR	NR	0	0	NR	NR
Stolte, 2018 ⁷⁷	After 4 loading doses	28	0	22 (81.5)	N/A	0	N/A	NR	N/A	0	N/A	0	N/A
NURTURE (presymptomatic)													
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018 ³⁷	Interim	25	N/A	25 (100)	N/A	9 (36)	N/A	0	N/A	0	N/A	0	N/A
Other													
Mercuri, 2017 ¹⁰³	247 patient-years	17 - presymptomatic	N/A	13 (76%)	N/A	5 (29%)	N/A	NR	NR	NR	NR	NR	NR
		100 - symptomatic infants	N/A	92 (92%)	N/A	72 (72%)	N/A	NR	NR	NR	NR	NR	NR

NA: not applicable, NR: not reported

Table D13. Harms II (Constipation, Fever, RSV, Respiratory Failure)

Study				URI-AE		Constipation		Pyrexia/Fever		RSV		Respiratory Failure	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatm ent, n (%)	Placebo, n (%)	Treatment , n (%)	Placebo, n (%)	Treatm ent, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017 ¹⁷	Final analysis	80	41	24 (30)	9 (22)	28 (35)	9 (22)	NR	NR	23 (29) pneumoni a; 5 (6) bronchitis viral; 6 (8) bronchitis	7 (17) pneumo nia	20 (25)	16 (39)
SHINE (OLE)													
Castro, 2018 ²⁶	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraz a, SHINE time only	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase 2													
Finkel, 2016 ¹⁶	32 months	4	16	3 (75)	11 (69)	1 (25)	8 (50)	3 (75)	11 (69)	1 (25) pneumoni a	6 (38) pneumo nia	NR	6 (38)
EMBRACE													
Shieh, 2018 ³⁶	14 months	14	7	5 (36)	2 (29)	NR	NR	6 (43)	1 (14)	NR	NR	NR	NR
Expanded Access Program (EAP)													
Pechman n, 2018 ⁷³	6 months	61	N/A	31 (58.5%)	NR	NR	NR	NR	NR	NR	NR	8 (15.1)	NR

Study				URI-AE		Constipation		Pyrexia/Fever		RSV		Respiratory Failure	
CL-101 (Zolgensma)													
Mendell, 2017 ²²	24 months - low dose	3	NR	1 (33)	NR	1 (33)	NR	1 (33)	NR	1 (33) pneumonia; 1 (33) bronchitis	NR	1 (33)	NR
	24 months - high dose	12	NR	10 (83)	NR	7 (58)	NR	6 (50)	NR	2 (17) pneumonia; 2 (17) bronchitis	NR	3 (25)	NR
Types II and III													
Mercuri, 2018 ¹⁸	Final analysis	84	42	25 (30)	19 (45)	NR	NR	36 (43)	15 (36)	NR	NR	NR	NR
Stolte, 2018 ⁷⁷	After 4 loading doses	28	0	1 (4)	N/A	2 (7)	N/A	NR	N/A	NR	N/A	NR	N/A
NURTURE (Presymptomatic)													
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018 ³⁷	Interim	25	N/A	NR	N/A	1 (4)	N/A	NR	N/A	NR	N/A	NR	N/A
Other													
Mercuri, 2017 ¹⁰³	247 patient-years	17 - presymptomatic	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	247 patient-years	100 - symptomatic infants	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Table D14. Harms III (Respiratory Distress, Nasopharyngitis, Headache, Other)

Study				Respiratory Distress		Atelectasis		Nasopharyngitis		Headache		Other	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n group (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017 ¹⁷	Final analysis	80	41	21 (26)	12 (29)	18 (22)	12 (29)	NR	NR	NR	NR	NR	NR
SHINE													
Castro, 2018 ²⁶	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraza, SHINE time only)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase 2													
Finkel, 2016 ¹⁶	32 months	4	16	1 (25)	6 (38)	NR	NR	NR	6 (38)	NR	NR	NR	NR
EMBRACE													
Shieh, 2018 ³⁶	14 months	14	7	NR	NR	NR	NR	3 (21) nasal congestion	0	NR	NR	4 (26) vomitin g; 7 (50) cough	1 (14) vomitin g; 1 (14) placebo
Expanded Access Program (EAP)													
Pechmann, 2018 ⁷³	6 months	61	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CL-101 (Zolgensma)													
Mendell, 2017 ²²	24 months - low dose	3	NR	NR	NR	0	NR	NR	NR	NR	NR	NR	NR
	24 months - high dose	12	NR	NR	NR	4 (33)	NR	NR	NR	NR	NR	NR	NR

Study				Respiratory Distress		Atelectasis		Nasopharyngitis		Headache		Other	
Types II and III													
Mercuri, 2018 ¹⁸	Final analysis	84	42	2 (2)	2 (5)	NR	NR	20 (24)	15 (36)	24 (29)	3 (7)	NR	NR
Stolte, 2018 ⁷⁷	After 4 loading doses	28	0	NR	N/A	NR	N/A	NR	N/A	17 (63)	N/A	6 (22.2) back pain ; 4 (14.8) nausea	N/A
NURTURE													
De Vivo, 2017 ¹⁰⁶	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	1 (Weight-loss)	NR
Swoboda, 2018 ³⁷	Interim analysis	25	N/A	NR	N/A	NR	N/A	NR	N/A	NR	N/A	NR	NR
OTHER													
Mercuri, 2017 ¹⁰³	247 patient-years	17 - presymptomatic	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		100 - symptomatic infants	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in this Analysis from... Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	<input type="checkbox"/>	<input type="checkbox"/>	
Medical Costs	Paid by third-party payers	X	X	Included within cost estimates
	Paid by patients out-of-pocket	X	X	Included in modified societal perspective to the extent possible
	Future related medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
	Future unrelated medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	<input type="checkbox"/>	
	Unpaid caregiver-time costs	NA	<input type="checkbox"/>	
	Transportation costs	NA	<input type="checkbox"/>	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Patient productivity gains included in modified societal perspective
	Cost of unpaid lost productivity due to illness	NA	<input type="checkbox"/>	
	Cost of uncompensated household production	NA	<input type="checkbox"/>	
Consumption	Future consumption unrelated to health	NA	<input type="checkbox"/>	
Social Services	Cost of social services as part of intervention	NA	<input type="checkbox"/>	
Legal/Criminal Justice	Number of crimes related to intervention	NA	<input type="checkbox"/>	
	Cost of crimes related to intervention	NA	<input type="checkbox"/>	
Education	Impact of intervention on educational achievement of population	NA	<input type="checkbox"/>	
Housing	Cost of home improvements, remediation	NA	X	
Environment	Production of toxic waste pollution by intervention	NA	<input type="checkbox"/>	
Other	Other impacts (if relevant)	NA	<input type="checkbox"/>	

NA: not applicable

Adapted from Sanders et al.¹⁰⁸

Estimating Proportions of “Sitting” Patients at Different Time Points on Spinraza

Whilst we know the proportion sitting among those who attended the follow up visits, we do not know the proportion of patients sitting among those who did not. Given this, we made an assumption that all the patients alive have the same likelihood to be in the ‘sitting’ health state i.e. the patients who did not attend the follow up have a similar proportion sitting as those who attended the follow up visits. Note that this is an assumption favorable to Spinraza as in reality it is likely that those who are in permanent ventilation have less likelihood to move to sitting health state compared to those who are in not sitting health state. As such, we multiplied the proportions of Spinraza patients alive at each of the time points and with the proportions of patients sitting at each time point to estimate the proportion sitting in Spinraza at different time points.

For estimating the proportion of Spinraza patients alive over time, we digitized the KM curve for OS in SHINE to estimate the survival at different time points. The manufacturer (Biogen) also provided us, as academic in confidence, data on number of patients deceased at each of the follow up visits. We used the data given by Biogen to estimate the proportion alive at the follow up visit time points and for the other time points we used the approximated survival estimates from the digitized KM curve.

As the data on proportion sitting in Castro et al poster is presented as integers, we followed a multi-stage process to estimate the true proportions of Spinraza patients sitting at the different time points. In step one, the numbers of patients sitting at each time point were estimated. In step two, these were rounded to the nearest integer. In step three, these integer values representing the number of patients sitting were divided by the number of patients at risk at each time point to estimate the true proportions of patients sitting. Also, to match with the model structure, the days at the follow up visits were converted into months and rounded to the nearest integer.

Table E2. Estimating Proportions of “Sitting” Patients at Different Time Points on Spinraza

	Baseline Month 0 n=81	Day 64 Month 2 n=70	Day 183 Month 6 n=65	Day 302 Month 10 n=51	Day 394 Month 13 n=48	Day 578 Month 19 n=31	Day 698 Month 23 n=17
% Achieving Independent Sitting (But Not Walking)	0	1	5	10	15	29	24
Step 1: Estimating Numbers of Patients at Each Period	0	0.7	3.25	5.1	7.2	8.99	4.08
Step 2: Rounding the Numbers to the Nearest Integer	0	1	3	5	7	9	4
Step 3: Proportion Sitting in Those Attending Follow Up	0.000	0.0143	0.0462	0.0980	0.1458	0.2903	0.2353
% Sitting	0.0000	0.0134	0.0399	0.0823	0.1206	0.2294	0.1859

Survival Modeling

The model used health state-specific mortality risks for the proportion of patients alive at the end of the short-term model. The long-term risk of mortality associated with each of the health states was modelled by fitting survival curves to the digitized published Kaplan-Meier (KM) data most relevant to each health state. For each health state, a single parametric distribution was selected to calculate the estimated probability of death in each time period (i.e. each month).

The KM data was digitized, and the individual data were reconstructed using the methods described in Guyot et al.⁸⁰ Different parametric distributions were fitted and the best fitting curves were identified based on a combination of: visual inspection, fit statistics such as Akaike information criteria (AIC)/Bayesian information criteria (BIC), and clinical plausibility.

The mortality risks associated with each health state are described in detail below.

Transitions from “Not Sitting” State

Patients from the “not sitting” state could transition to either the “permanent ventilation” health state or to death. At each monthly cycle, the ventilation free survival (VFS) curve was subtracted from the OS curve to estimate the proportion of patients in the “permanent ventilation” health state.

The source of data available to model these (i.e., VFS and OS) of SMA Type I patients was the sham control arm of the ENDEAR trial (n=41), with a follow-up of 52 weeks. In the model analysis plan (MAP), it was proposed to use NeuroNEXT data to estimate these transition probabilities; however, it had a smaller sample size compared to the sample size of the sham control arm in the ENDEAR trial. As such, we used the parametric distributions fitted to the data from sham control arm of ENDEAR¹⁷. Exponential distributions were selected to model the VFS and OS based on clinical plausibility, visual fit, and AIC/BIC.

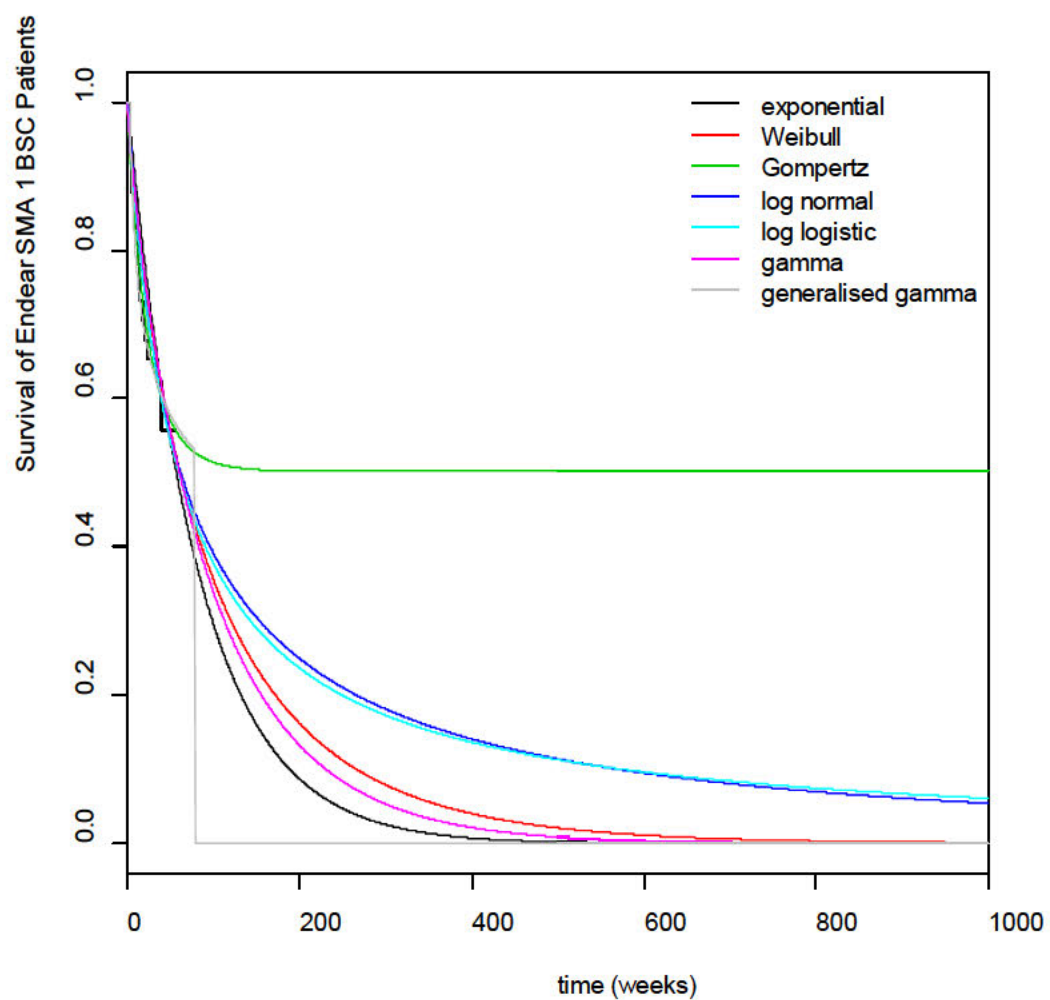
Not Sitting to Death

Table E3. Fit Statistics for Parametric Distributions Fitted to Overall Survival of Sham Control Arm in ENDEAR¹⁷

Distribution	AIC	BIC
Exponential	185.79	187.50
Weibull	186.86	190.28
Gompertz	183.72	187.15
Log-Normal	183.87	187.29
Log-Logistic	185.42	188.85
Gamma	187.21	190.63
Generalized Gamma	180.00	185.14

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E1. Parametric Distributions Fitted to Overall Survival of Sham Control Arm in ENDEAR¹⁷.



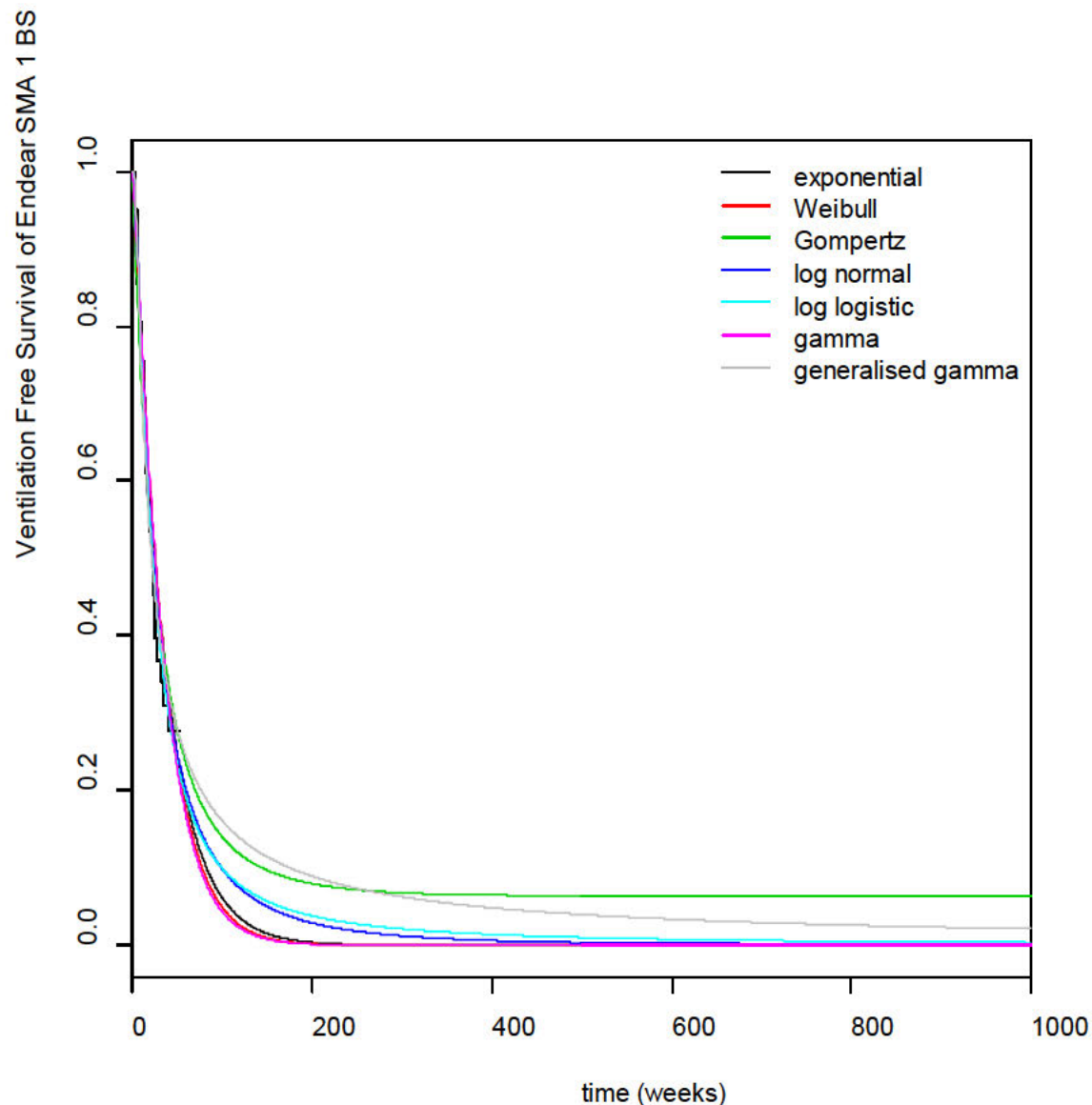
Not Sitting to Death or Permanent Ventilation

Table E4. Fit Statistics for Parametric Distributions Fitted to Ventilation Free Survival of Sham Control Arm in ENDEAR¹⁷.

Distribution	AIC	BIC
Exponential	258.27	259.99
Weibull	260.11	263.54
Gompertz	259.48	262.91
Log-Normal	255.25	258.68
Log-Logistic	256.20	259.62
Gamma	259.69	263.12
Generalized Gamma	255.77	260.91

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E2. Parametric Distributions Fitted to Sham Control Arm in ENDEAR¹⁷.



Mortality in Permanent Ventilation Health State

The Gregoret et al. study, which was a retrospective data analysis⁴⁰ of SMA Type I patients from four Italian centers from October 1992 to December 31, 2010, presented survival data for SMA Type I patients on permanent ventilation. In the MAP, we proposed to use data from two patient cohorts reported in this retrospective study: a) patients with continuous non-invasive respiratory muscle aid, including non-invasive ventilation, and mechanically assisted cough (n=31), represented as the NRA curve in the figure below, and b) patients with tracheostomy and invasive mechanical ventilation (n=42), represented as the TV curve. The curve NT represents the no treatment arm.

However, seven patients received tracheostomy in the NRA arm and the study did not present any details about whether the data presented for the NRA arm were after censoring for these patients or including these patients. Furthermore, they also did not present the numbers at risk for either arm, so it was difficult to understand the robustness of these survival estimates. The study also did not provide the reasons for patients receiving different treatments and it is possible that the survival estimates would be confounded (for example, if patients with less-severe disease received a specific treatment such as TV).

Given all these issues, the NRA curve alone was used to model the mortality risk from the permanent ventilation state. Different parametric curves were fitted and exponential distribution was chosen based on visual inspection, fit statistics (AIC/BIC), and clinical plausibility.

Figure E3. Parametric Distributions Fitted to NRA Arm in Gregoretti et al.⁴⁰

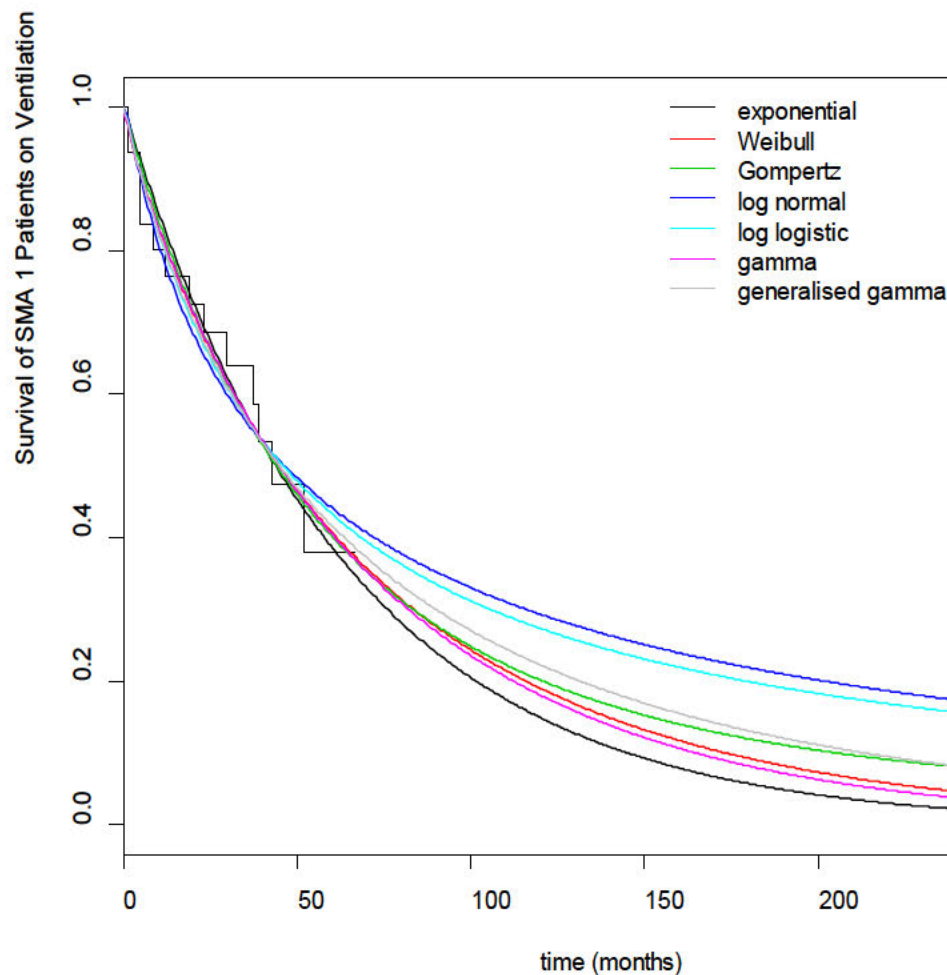


Table E5. Fit Statistics for Parametric Distributions Fitted to NRA Arm in Gregoretti et al.

Distribution	AIC	BIC
Exponential	146.07	147.50
Weibull	147.78	150.65
Gompertz	148.00	150.87
Log-Normal	147.95	150.82
Log-Logistic	148.13	151.00
Gamma	147.79	150.65
Generalized Gamma	149.78	154.08

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

SMA Type II (Sitting)

Treated SMA Type I patients who can sit were assumed to have similar prognosis as SMA Type II patients, who are able to sit but not walk. Pooled data from German and Polish studies on SMA Type II patients (n=240) presented in Zerres and Schöneborn et al.⁴¹ were used to model the mortality from the “sitting” health state.

The original KM curve was digitized, and the individual data were reconstructed using the methods described in Guyot et al.⁸⁰ The KM curve has substantial censoring in the early time periods and the study did not report the numbers at risk at different time periods. In the absence of numbers at risk at different time periods, the algorithm in Guyot et al.⁸⁰ assumes that the censoring is constant over the entire time period. As such, the algorithm estimates that all the events happened within 25 years (see figure below). That is, it only outputs part of the K-M curve.

This issue can be addressed by using educated approximations of the numbers at risk at different time points. For example, when assuming the number at risk at 10 years to be 100, the algorithm estimated a bigger proportion of the KM curve. This can be extended even further by assuming that the number at risk at 10 years to be 80, where the algorithm estimated the whole of the KM curve.

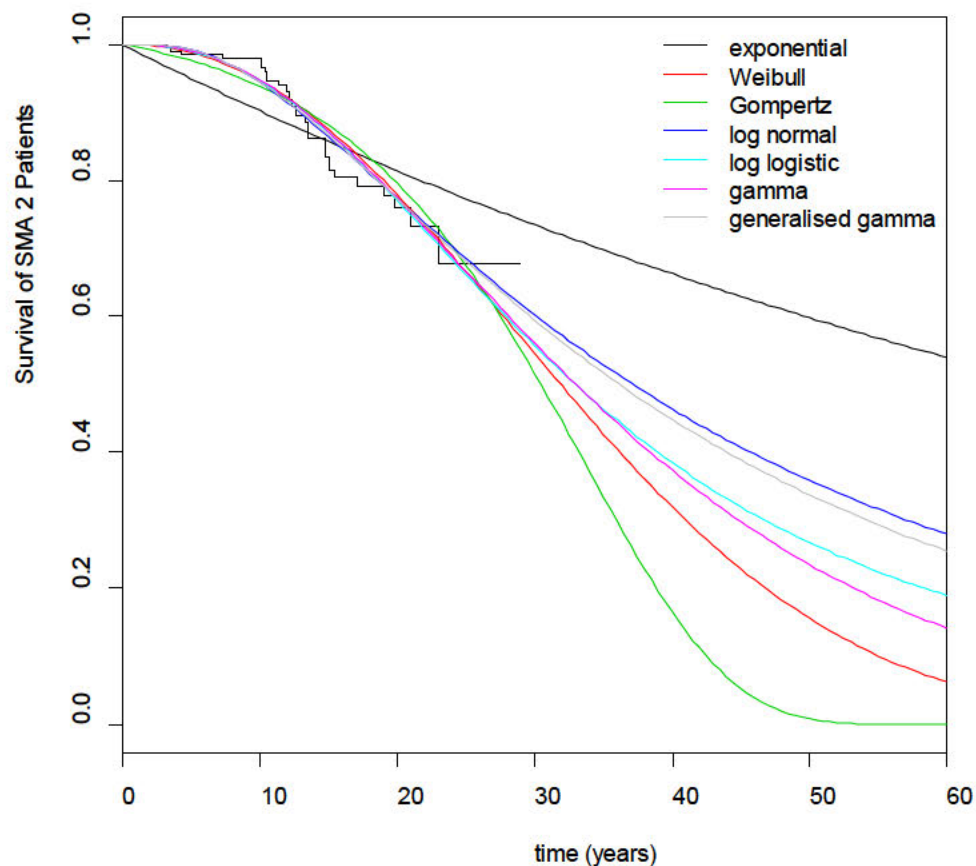
However, the numbers of patients at risk in the later parts of the curve (e.g., after 25 years) seems quite low as each event caused a large difference to the survival curve. Given these patients were outliers, after discussions with survival modelling experts, we decided to use the first analysis, only fitting to the early part of the KM curve as estimated by the algorithm in Guyot et al.⁸⁰ assuming constant censoring over the entire time period. Different parametric curves were fitted and Gompertz distribution was chosen based on visual inspection, fit statistics (AIC/BIC), and clinical plausibility.

Table E6. Fit Statistics for Parametric Distributions Fitted to Survival of SMA Type II Patients in Zerres and Schöneborn et al.⁴¹

Distribution	AIC	BIC
Exponential	347.86	351.34
Weibull	327.96	334.92
Gompertz	335.64	342.60
Log-normal	325.92	332.88
Log-logistic	326.50	333.46
Gamma	326.53	333.49
Generalized Gamma	327.89	338.33

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E4. Parametric Distributions Fitted to Survival of SMA Type II Patients in Zerres and Schöneborn et al.⁴¹



Patient Productivity Gains

No productivity changes were assumed for those in the “permanent ventilation” and “not sitting” health states. For other health states, data from the Lewin Group report⁹¹ on educational attainment for SMA patients were combined with data on income by education level in the US from the Bureau of Labor Statistics⁹² to estimate the productivity gains of patients. These proportions were weighted by monthly earnings to estimate the potential monthly income as \$4,450, as shown in Table E7 below. These productivity gains were estimated from the age of 30 years until an age of 65 years.

Table E7. Patient Productivity Gains

Education Level	Numbers (n) (N=188)	Proportions (i.e., n/N)	Weekly Earnings*
Data Not Available	8	0.0426	\$520†
Less than High School	8	0.0426	\$520
High School Graduate	28	0.1489	\$712
Some College/Associate Degree/Post-High School Education	56	0.2979	\$836
College Graduate	51	0.2713	\$1,173‡
Post-Graduate	37	0.1968	\$1,660§
Potential Monthly Income	\$4,450		

*<https://www.bls.gov/emp/tables/unemployment-earnings-education.htm>.

†Assumed to be the earnings of those who have less than high school diploma.

‡Assumed to be the earnings from bachelor’s degree.

§Assumed to be average of earnings from master’s degree, professional degree, and doctoral degree.

Modified Societal Perspective Including Caregiver Burden

As the methods for performing economic evaluation including caregiver burden are still under development, we present here our thoughts on considerations and methodologies for performing a modified societal perspective analysis that includes caregiver burden.

Bastida et al. in 2017¹⁰⁹ surveyed 81 caregivers of patients with different subtypes of SMA in Spain, and reported that the mean utility of all caregivers, estimated using the EuroQol-Five Dimension (EQ-5D) questionnaire with the time trade-off method, was 0.484. Out of 81 patients, eight had SMA Type I, 60 had SMA Type II, and 13 had SMA Type III.¹⁰⁹ They also reported the mean utility value for Type II patients as 0.472, as shown in Table E8.

Given the very low utility values reported, there were concerns with the face validity of this data. We thus used the baseline utility of 0.484 for caregivers of patients in the “permanent ventilation” health state and assumed that the utility for those caring for patients in the “walking” health state

was 0.878 (i.e., the same as the patients themselves). The utility values for caregivers of patients in “not sitting” and “sitting” health states were estimated by assuming a slope of increasing utility. The difference between the “walking” and “permanent ventilation” health states (i.e., 0.878-0.484) was estimated and a quarter of this difference was added to the utility of the “permanent ventilation” health state to get the utility for the “not sitting” health state; and half of this difference was added to the utility of the “permanent ventilation” health state to derive the utility for the “sitting” health state. The utility values estimated for caregivers are presented in Table E8.

We would assume that there are two caregivers for each patient. Also, caregiver disutilities would be used instead of an added utility approach, because we do not know caregiver disutility after the death of an SMA patient or the duration of this disutility; hence, we would propose using disutilities instead of an added utility approach. In each health state, caregiver disutilities would be estimated by subtracting the utility of caregivers in the “walking” health state (i.e., 0.878) from the utility of the caregivers in that health state. Table E8 presents the caregiver disutilities in the societal perspective analyses that includes caregiver burden.

This could result in negative QALYs due to the fact that the disutility of the caregivers (-0.394) is higher than the utility for the patients (0.19 for the “not sitting” and “permanent ventilation” states).

Table E8. Caregiver Utility Values

Health State	Caregiver Utility	Description	Caregiver Disutility
Permanent Ventilation	0.484	Assumption	-0.394
Not Sitting	0.583	Assumption	-0.2955
Sitting	0.681	Assumption	-0.197
Walking	0.878	Assumption	0

Lost Household Income

The Lewin Group report⁹¹ estimated lost household income from caring for SMA patients using regression analyses. Two different estimates for lost family income were presented: estimate one was of lost household income directly; estimate two used the difference between potential and current income as an estimate of the lost household income. Scenario analyses would be performed using both estimates in Table E9.

Table E9. Lost Household Income

	Estimate 1		Estimate 2	
	SMA Early Onset	SMA Other	SMA Early Onset	SMA Other
Predicted Loss	\$19,833	\$14,800	\$39,783	\$12,407
Standard Error	\$13,633	\$3,557	\$2,750	\$700

Breakdown of the SMA Type I Model Results

The breakdown of the LYs, QALYs, and costs according to health state for the different interventions in the SMA Type I population are presented here. Table E10 presents the breakdown for LYs. As can be observed, the majority of the LYs and QALYs gained are in the “sitting” and “walking” health states. This is because of the longer survival associated with these health states compared with the “not sitting” and “permanent ventilation” health states (Figure E3). None of the patients in BSC arm achieved milestones, and as such the LYs achieved in this arm were lower compared with the treatment arms. In the Spinraza arm, around 19% of the patients were in the sitting health state at the end of the short-term model, which provided 5.32 LYs, while in the Zolgensma arm approximately 62.5% of the patients were in the sitting health state, which provided 17.84 LYs. The Zolgensma arm also had approximately 16.7% in the walking health state at the end of the short-term model, which provided a further 12.93 LYs. This is as expected, as the model assumed that those in the walking health state have general population mortality.

Table E10. Undiscounted LYs by Health State in the SMA Type I Model

Undiscounted LYs	Ventilated	Not Sitting	Sitting	Walking	Total Undiscounted LYs
BSC	1.99	0.70	0.00	0.00	2.68
Spinraza	2.23	2.73	5.32	0.00	10.28
Zolgensma	0.00	2.36	17.84	12.93	33.13

LY: life-year

The breakdown of the discounted LYs and QALYs according to health state for the different interventions are presented in Tables E11 and E12. These results follow the same pattern as Table E10, but the absolute numbers are lower due to discounting (for discounted LYs) and the use of QoL weights (see Table 4.5) for discounted QALYs. The utility values in the “not sitting” and “permanent ventilation” health states were 0.19, resulting in quite low QALYs for BSC. For Spinraza and Zolgensma, the majority of the QALYs are from the patients in the “sitting” health state, who have a utility of 0.6. As before, Zolgensma also had a proportion of patients (16.7%) who were in the “walking” health state at the end of short-term model, but they contributed over 33% of the total QALYs. This is because the utility in the walking health state is the same as general population utilities, which are much higher than utilities in the other health states.

Table E11. Discounted LYs by Health State in the SMA Type I Model

Discounted LYs	Ventilated	Not Sitting	Sitting	Walking	Total Discounted LYs
BSC	1.71	0.68	0.00	0.00	2.40
Spinraza	1.89	2.40	3.36	0.00	7.64
Zolgensma	0.00	2.13	11.27	4.77	18.17

LY: life-year

Table E12. Discounted QALYs by Health State in the SMA Type I Model

Discounted QALYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted QALYs
BSC	0.33	0.13	0.00	0.00	0.46
Spinraza	0.36	0.70	2.18	0.00	3.24
Zolgensma	0.00	0.62	7.32	4.29	12.23

QALY: quality adjusted life-year

The breakdown of the discounted costs according to health state for the different interventions are presented in Table E13. The costs are broken out into treatment costs, administration costs, and non-treatment health care costs.

For Spinraza and Zolgensma, as seen in Table E13, treatment costs made up the majority of overall costs. In the Spinraza arm, treatment costs were broadly proportional to the LYs gained in each health state; it should be noted that the model assumed that treatment is discontinued after 24 months for patients who do not achieve milestones (i.e., the patients in the “not sitting” and “permanent ventilation” states). Zolgensma was modeled as a one-time upfront cost.

For BSC, health care costs were associated only with patients in the “not sitting” and “permanent ventilation” health states. The costs of permanent ventilation were higher for BSC, reflecting the longer survival of these patients.

Regarding the non-treatment health care costs, for Spinraza and Zolgensma, most of the costs associated with the “sitting” health state were accrued in the short-term model, due to most patients starting in this state (while they achieve the milestones) and to these costs not being affected by discounting, as they are accrued at the beginning of the model. Again, the costs of permanent ventilation were higher for Spinraza, reflecting the longer survival of these patients. For Zolgensma, although none of the patients in the Zolgensma study received permanent ventilation, the long-term model included a proportion of patients in the “not sitting” health state who were simulated to move into permanent ventilation and have costs in that state. Furthermore, in the Zolgensma treatment arm, the patients in the “sitting” and “walking” health states had more LYs and accrued further costs, even though the costs associated with those health states (\$6,357 and \$2,499 per month, respectively) were lower than costs associated with the “not sitting” and “permanent ventilation” health states (\$25,517 and \$28,218 per month, respectively).

Table E13. Breakdown of the Discounted Costs by Health State

Treatment Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	\$156,569	\$794,619	\$1,279,642	--	\$2,230,829
Zolgensma	--	\$2,000,000*	--	--	\$2,000,000
Administration Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	\$1,485	\$7,535	\$12,134	--	\$21,154
Zolgensma	--	\$137	--	--	\$137
Health Care Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	\$580,684	\$208,793	--	--	\$789,477
Spinraza	\$641,516	\$733,869	\$256,173	--	\$1,631,557
Zolgensma	\$1,375	\$653,126	\$859,378	\$143,123	\$1,657,002

*Placeholder price.

Probabilistic Sensitivity Analyses Results for Type I SMA Model

This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis (PSA) for the Spinraza versus BSC comparison in Type I SMA model. Due to the lack of data, the distributions used for costs and utilities in the PSA are mean values $\pm 10\%$. Figure E5 below presents the cost-effectiveness clouds (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Spinraza versus BSC in the Type I SMA Model.

Figure E5. Cost-Effectiveness Clouds for Spinraza versus BSC in Type I SMA Model

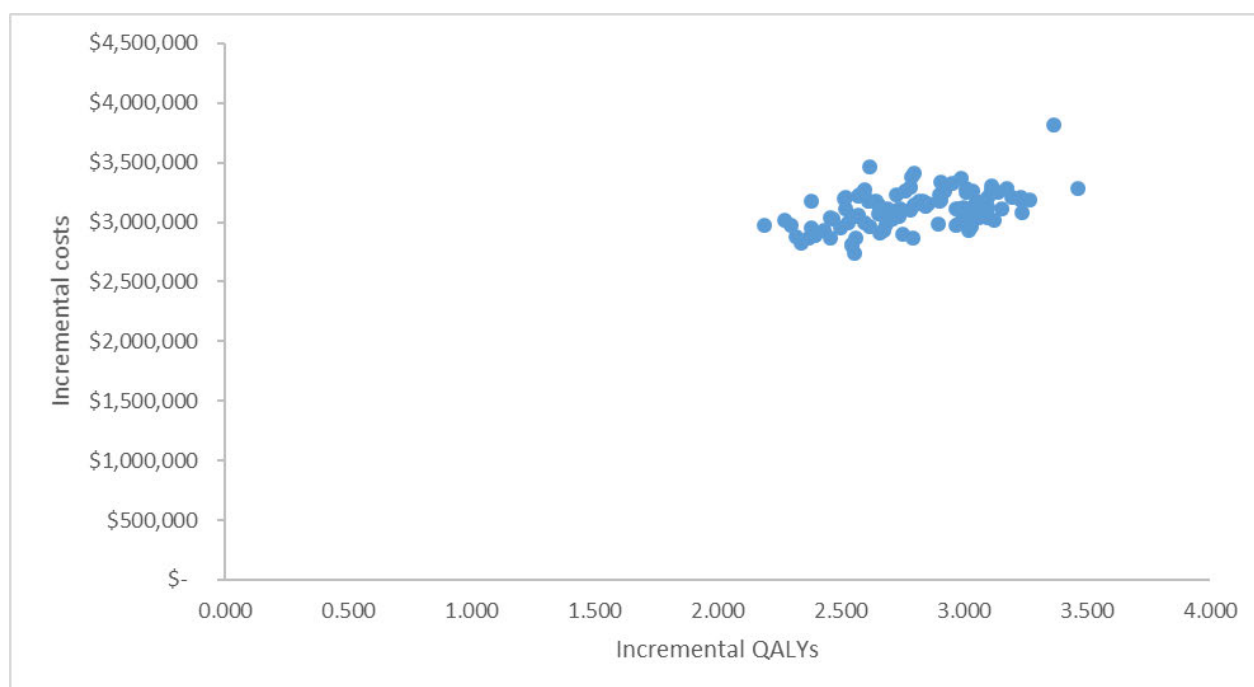


Figure E6 below presents the cost-effectiveness acceptability curve for Spinraza versus BSC in the Type I SMA Model. Spinraza had no likelihood of being cost-effective at thresholds less than \$500,000 per QALY.

Figure E6. Cost-Effectiveness Acceptability Curve for Spinraza versus BSC in Type I SMA Model

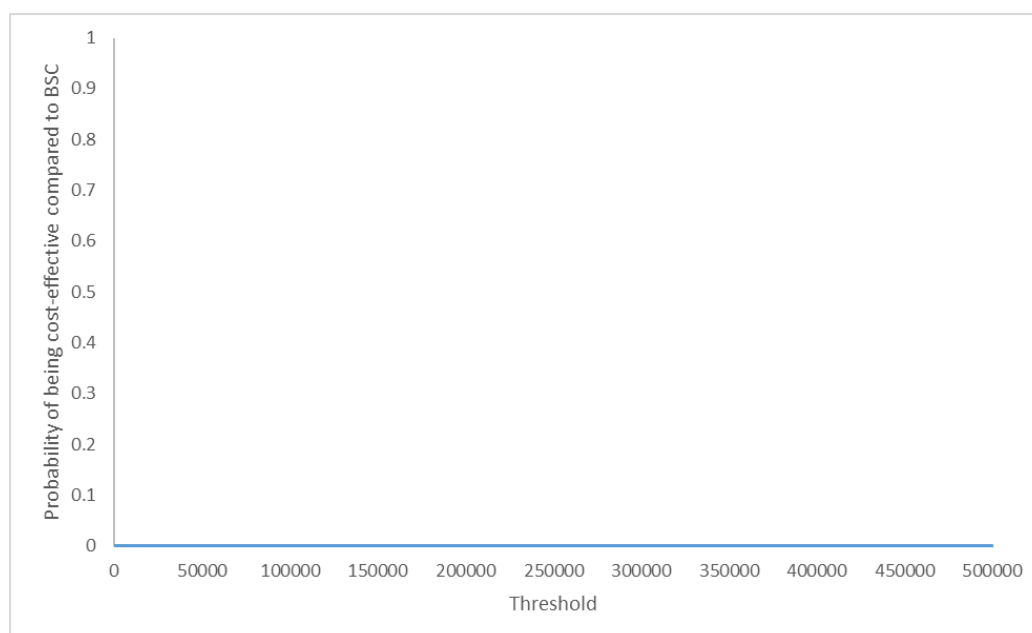


Figure E7 below presents the cost-effectiveness cloud (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Zolgensma versus BSC in the Type I SMA Model.

Figure E7. Cost-Effectiveness Clouds for Zolgensma versus BSC in Type I SMA Model

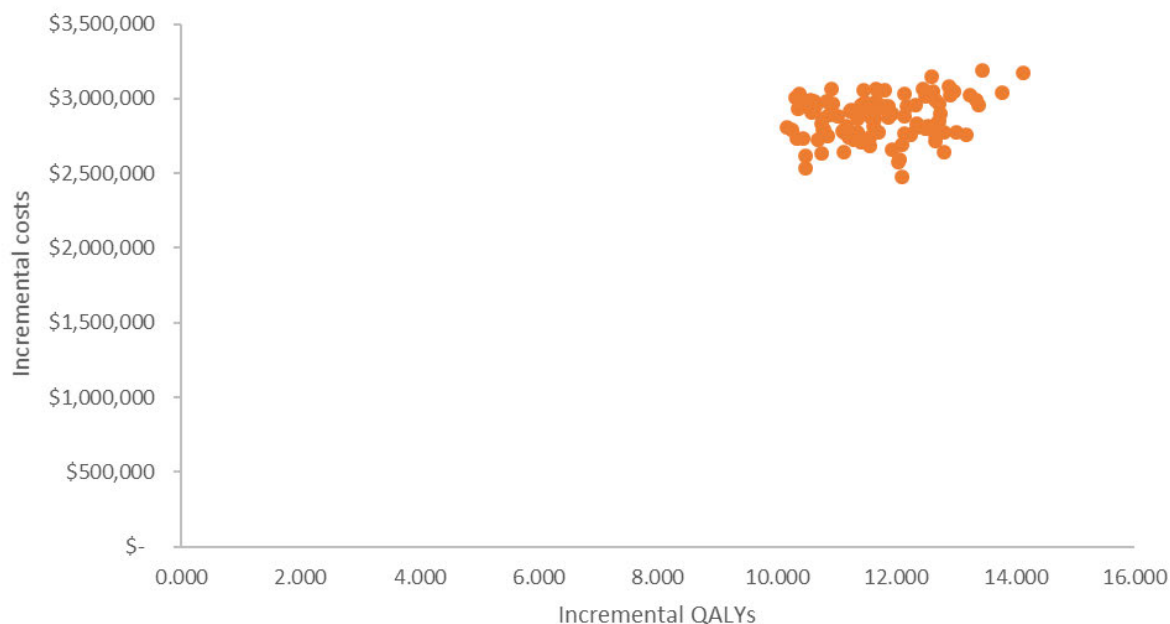
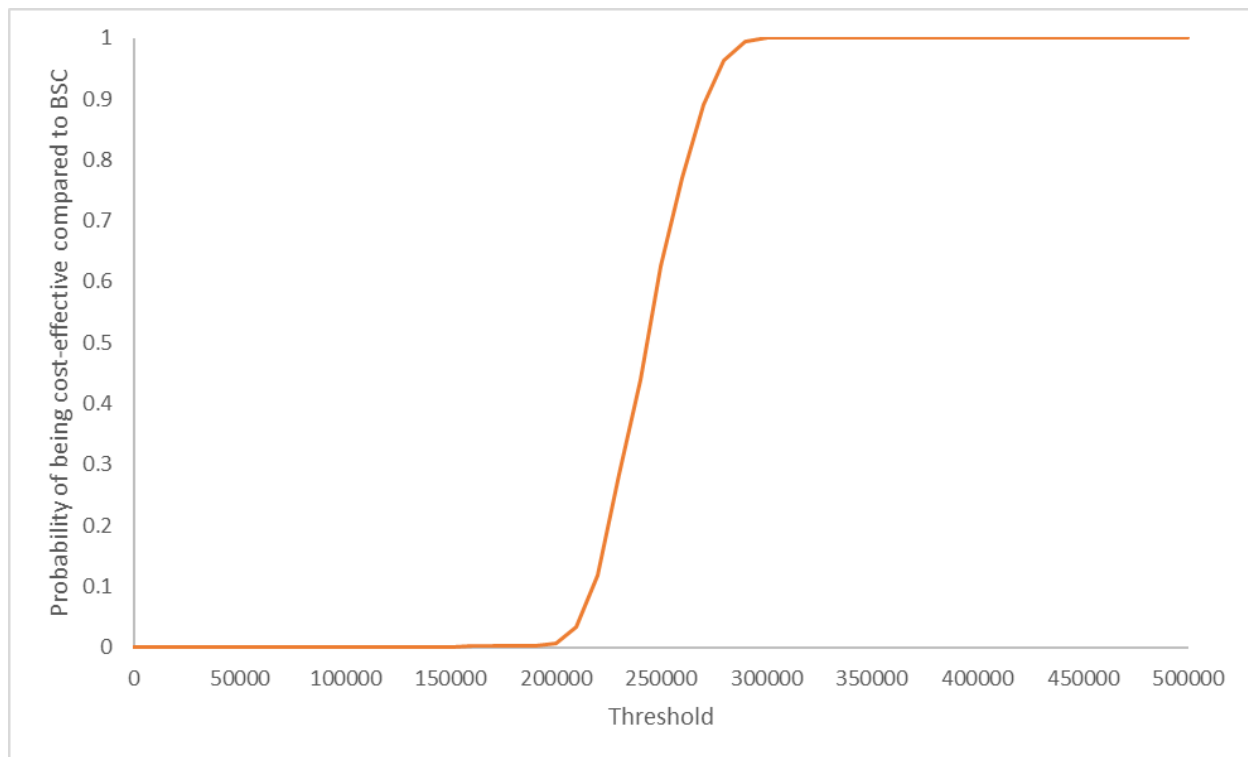


Figure E8 presents the cost-effectiveness acceptability curve for Zolgensma versus BSC in the Type I SMA Model. Zolgensma had a 0.1% chance of being cost effective at a threshold of \$150,000 per QALY but 100% chance of being cost-effective at thresholds above \$300,000 per QALY gained.

Figure E8. Cost-Effectiveness Acceptability Curve for Zolgensma versus BSC in Infantile-Onset (Type I) SMA Model



Scenario Analyses Results for Type I SMA Model

We performed several scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results. In scenario analysis #1, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. In scenario analysis #2, we used lower health state costs of \$10,434 for the “not sitting” health state and \$13,135 for the “permanent ventilation” health state. In scenario analysis #3, we used lower utilities of 0.5 for the “sitting” health state and 0.7 for the “walking” health state. In scenario analysis #4, we assumed roughly half the mean survival for the “sitting” and “walking” health states. This led to a mean survival of 15.6 years and 39.65 years for the “sitting” and “walking” health states, respectively. This scenario was implemented using HRs of five and 16 to the survival curves for “sitting” and “walking” health states, respectively. Also, for face validity, we imposed a constraint that the survival in “sitting” health state cannot be greater than “walking” health state.

In scenario analysis #5, we used the assumptions in scenarios #3 and #4 together (i.e., both roughly half the mean survival and lower utilities for the “sitting” and “walking” health states).

Scenario analysis #6 was only relevant to Zolgensma versus BSC, where we assumed that none of the patients in the Zolgensma arm received Spinraza and there was no loss of milestones assumed after the short-term model, as a proxy for receiving Spinraza.

We have also conducted scenario analyses assuming a proportion of the patients in the “sitting” health state would lose their milestones (scenario analyses #7a to #7c). We tested a range of proportions from 10% to 30%. Finally, given the lack of long-term follow up and the optimistic assumptions used in the base-case analysis, we have also conducted analyses for a “pessimistic” scenario, which assumed 30% of the patients in the “sitting” health state lose milestones while also assuming lower survival and utilities for those in the “sitting” health state.

Scenario analysis #8 uses a 10-year time horizon and scenario analysis #9 uses 1.5% discount rate for both costs and QALYs.

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as a utility of 0.19 for the “not sitting” health state and a utility of 0.65 for the “sitting” health state for both BSC and treatment arms.

Tables E14 and E15 present the results for the health care sector perspective for this scenario analysis. Table E14 presents the results for Spinraza versus BSC while Table E15 presents results for Zolgensma versus BSC. As expected, the QALY gains in the Spinraza and Zolgensma arms are lower, resulting in higher incremental cost-effectiveness ratios compared to the base-case analyses.

Table E14. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	2.83	7.64	\$1,303,000	\$590,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E15. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,657,000	\$3,657,000	11.46	18.17	\$261,000	\$182,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation Health States – Health Care Sector Perspective

Tables E16 and E17 present the results for the health care sector perspective for the scenario analysis assuming lower costs of \$10,434 for the “not sitting” health state and \$13,135 for the “permanent ventilation” health state. Table E16 presents the results for Spinraza versus BSC while Table E17 presents results for Zolgensma versus BSC.

Table E16. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$877,000	\$3,108,000	3.24	7.64	\$990,000	\$525,000
BSC	--	\$356,000	\$356,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E17. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,271,000	\$3,271,000	12.23	18.17	\$248,000	\$185,000
BSC	--	\$356,000	\$356,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Health Care Sector Perspective

Tables E18 and E19 present the results for the health care sector perspective for the scenario analysis assuming lower utilities of 0.5 for the “sitting” health state and 0.7 for the “walking” health state. Table E18 presents the results for Spinraza versus BSC while Table E19 presents the results for Zolgensma versus BSC.

Table E18. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	2.90	7.64	\$1,265,000	\$590,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E19. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,657,000	\$3,657,000	10.16	18.17	\$296,000	\$182,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Health Care Sector Perspective

Tables E20 and E21 present the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival for the “sitting” and “walking” health states, a mean survival of 15.6 years and 39.65 years for the “sitting” and “walking” health states, respectively. This scenario was implemented using HRs of 5 and 16 to the survival curves for “sitting” and “walking” health states, respectively. Also, for face validity, we imposed a constraint that the survival in “sitting” health state cannot be greater than “walking” health state. Table E20 presents the results for Spinraza versus BSC while Table E21 presents the results for Zolgensma versus BSC.

Table E20. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,807,000	\$1,564,000	\$3,371,000	2.52	6.53	\$1,253,000	\$624,000
BSC	--	\$790,000	\$790,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E21. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,340,000	\$3,340,000	8.87	13.34	\$303,000	\$233,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Survival and Lower Utility for Sitting and Walking Health States – Health Care Sector Perspective

Tables E22 and E23 present the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival and lower utilities for the “sitting” and “walking” health states. Table E22 presents the results for Spinraza versus BSC while Table E23 presents the results for Zolgensma versus BSC.

Table E22. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,807,000	\$1,564,000	\$3,371,000	2.29	6.53	\$1,407,000	\$624,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E23. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,340,000	\$3,340,000	7.34	13.34	\$371,000	\$233,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Using No Loss of Milestones in Zolgensma as a Proxy for Spinraza Follow-On Therapy – Health Care Sector Perspective

In this scenario, no patients in the Zolgensma arm were assumed to drop any milestones. This is to understand the effect of dropping the assumption made in the base-case analyses that 16.7% in the “sitting” health state drop a milestone, as a proxy for receiving Spinraza add-on therapy. Table E24 presents the results for the health care sector perspective for this scenario analysis.

Table E24. Results for Scenario Analysis Assuming No Loss of Milestones in Zolgensma as a Proxy for Spinraza Follow-On Therapy: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,655,000	\$3,655,000	13.46	19.76	\$220,000	\$165,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming 10% Loss of Milestones in “Sitting” Health State for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

In this scenario, 10% of the patients in the “sitting” health state of the Spinraza arm were assumed to drop a milestone. This scenario was only performed for Spinraza as the base-case analyses for Zolgensma already assumes 16.7% of the patients in the “sitting” state lose a milestone at the end of the short term model. Table E25 presents the results for the health care sector perspective for this scenario analysis comparing Spinraza to BSC.

Table E25. Assuming 10% of Patients in the “Sitting” Health State Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,114,000	\$1,652,000	\$3,766,000	3.06	7.41	\$1,143,000	\$593,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 20% Loss of Milestones in “Sitting” Health State for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

In this scenario, 20% of the patients in the “sitting” health state of the Spinraza arm were assumed to drop in milestones. Table E26 presents the results for the health care sector perspective for this scenario analysis.

Table E26. Assuming 20% of Patients in the “Sitting” Health State Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,996,000	\$1,652,000	\$3,648,000	2.88	7.18	\$1,178,000	\$597,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 20% Loss of Milestones in “Sitting” Health State for Zolgensma versus BSC in Type I – Health Care Sector Perspective

In this scenario, 20% of the patients in the “sitting” health state of the Zolgensma arm were assumed to drop in milestones. Table E27 presents the results for the health care sector perspective for this scenario analysis.

Table E27. Assuming 20% of Patients in the “Sitting” Health State Lose Milestone at the End of the Short-Term Model for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,658,000	\$3,658,000	11.99	17.85	\$249,000	\$186,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

*Placeholder price.

Scenario Analysis Assuming 30% Loss of Milestones in “Sitting” Health State for Spinraza versus BSC in Type I – Health Care Sector Perspective

In this scenario, 30% of the patients in the “sitting” health state of the Spinraza arm are assumed to drop in milestones. Table E28 presents the results for the health care sector perspective for this scenario analysis.

Table E28. Assuming 30% of Patients in the “Sitting” Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,879,000	\$1,651,000	\$3,530,000	2.70	6.95	\$1,218,000	\$601,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 30% Loss of Milestones in “Sitting” Health State for Zolgensma versus BSC in Type I – Health Care Sector Perspective

In this scenario, 30% of the patients in the “sitting” health state of the Zolgensma arm are assumed to drop in milestones. Table E29 presents the results for the health care sector perspective for this scenario analysis.

Table E29. Assuming 30% of Patients in the “Sitting” Lose Milestone at the End of the Short-Term Model for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,659,000	\$3,659,000	11.25	16.90	\$266,000	\$198,000
BSC	--	\$790,000	\$790,000	0.46	2.40	--	--

*Placeholder price.

Pessimistic Scenario Analysis Assuming 30% Loss of Milestones in “Sitting” Health State and Assuming Lower Survival and Utilities for Sitting Health States for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

Given the lack of long-term follow up and the optimistic assumptions used in the base-case analysis, we also conducted a “pessimistic scenario,” which assumes 30% of patients in the “sitting” health state lose milestones as well as lower survival and utilities for those in the “sitting” health states. Although the assumptions about “walking” health state are changed to ensure consistency with the scenario analysis in Zolgensma arm, they do not affect the results as there are no patients in the “walking” health state in the Spinraza arm. Table E30 presents the results for the health care sector perspective for this scenario analysis. Note that this pessimistic scenario still includes the utility benefit in the treatment arms for achieving interim milestones.

Table E30. Pessimistic Scenario assuming 30% of Patients in the “Sitting” Health State Lose Milestone at the End of the Short-Term Model and Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,582,000	\$1,589,000	\$3,171,000	2.03	6.18	\$1,509,000	\$630,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

Table E31 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E31. Pessimistic Scenario assuming 30% of Patients in the “Sitting” Health State Lose Milestone at the End of the Short-Term Model and Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,387,000	\$3,387,000	6.85	12.67	\$406,000	\$253,000
BSC	--	\$789,000	\$789,000	0.46	2.40	--	--

*Placeholder price.

Scenario Analysis Using 10-Year Time Horizon – Health Care Sector Perspective

Tables E32 and E33 present the results for the health care sector perspective for the scenario analysis using a 10-year time horizon. Table E32 presents the results for Spinraza versus BSC while Table E33 presents the results for Zolgensma versus BSC.

Table E32. Using a 10-Year Time Horizon for Spinraza versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,484,000	\$1,338,000	\$2,822,000	1.85	5.21	\$1,460,000	\$700,000
BSC	--	\$727,000	\$727,000	0.42	2.21	--	--

Table E30 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E33. Using a 10-Year Time Horizon for Zolgensma versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,005,000	\$3,005,000	4.76	7.91	\$525,000	\$400,000
BSC	--	\$727,000	\$727,000	0.42	2.21	--	--

*Placeholder price.

Scenario Analysis Using 1.5% Discounting for Costs and QALYs – Health Care Sector Perspective

Tables E34 and E35 present the results for the health care sector perspective for the scenario analysis using 1.5% discounting for both costs and QALYs. Table E34 presents the results for Spinraza versus BSC while Table E35 presents the results for Zolgensma versus BSC.

Table E34. Using 1.5% Discounting for Spinraza versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,549,000	\$1,818,000	\$4,368,000	3.84	8.77	\$1,052,000	\$566,000
BSC	--	\$834,000	\$834,000	0.48	2.53	--	--

Table E35 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E35. Using 1.5% Discounting for Zolgensma versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,976,000	\$3,976,000	16.29	23.62	\$199,000	\$149,000
BSC	--	\$834,000	\$834,000	0.48	2.53	--	--

*Placeholder price.

Later-Onset SMA Model

In the later-onset SMA model, based on the CHERISH trial data, all patients are assumed to be in the “sitting” health state. As such, no breakdown of the costs, LYs, and QALYs by health state is provided.

Scenario Analyses Results – Later Onset SMA Model

Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Health Care Sector Perspective

This scenario included further utility benefits in the Spinraza arm for achieving interim milestones such as standing, walking with assistance, etc. This was implemented in the model as a utility of 0.7 for the “sitting” health state for the Spinraza arm (i.e., an additional utility of 0.1 compared to BSC).

Table E36 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALY gains in the Spinraza arm were higher, resulting in a more favorable cost-effectiveness ratio compared to base-case analyses.

Table E36. Results for Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$7,634,000	\$1,514,000	\$9,148,000	13.23	18.90	\$4,078,000	Dominated
BSC	--	\$1,442,000	\$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Stopping Spinraza after Two Years – Health Care Sector Perspective

Here, we assumed that the Spinraza treatment was stopped after two years. We also assumed a utility benefit (as in the base case) for achieving interim milestones in the Spinraza arm (i.e., utility of 0.65 for the “sitting” health state in the Spinraza arm, and an additional utility of 0.05 compared to BSC). Table E37 presents the results for the health care sector perspective for this scenario analysis. As expected, the treatment costs in the Spinraza arm were lower, resulting in more favorable cost-effectiveness ratios compared to base-case analyses.

Table E37. Results for Scenario Analysis Assuming stopping Spinraza after Two Years and Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$1,127,000	\$1,452,000	\$2,579,000	12.28	18.90	\$1,204,000	Dominated
BSC	--	\$1,442,000	\$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as standing, crawling, etc. This was implemented in the model as a utility of 0.65 for the “sitting” health state for the Spinraza and the BSC arms. Table E38 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALYs in the Spinraza arm and BSC arm are the same, resulting in Spinraza being dominated.

Table E38. Results for Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$7,634,000	\$1,514,000	\$9,148,000	11.34	18.90	Dominated	Dominated
BSC	--	\$1,442,000	\$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Presymptomatic SMA Model

Breakdown of the Presymptomatic SMA Model Results

The breakdown of LYs according to health state for the different interventions are presented below in Table E39. As can be observed, a majority of the LYs gained were in the “sitting” and the “walking” health states. This was because of the longer survival associated with these health states compared to “not sitting” and “permanent ventilation” states (see Figure 4.3).

In the BSC arm, as the baseline population included 30% of patients who have SMA Type II (i.e., patients in the “sitting” state) and 10% of patients who have SMA Type III (i.e., patients with survival similar to general population), this was where the majority of LYs were accrued in the BSC arm (8.79 LYs and 7.87 LYs in the “sitting” and “walking” health states, respectively). In the Spinraza arm, a majority of the patients were in the walking state at the end of the short term model, which was where the majority of LYs were accrued (52.9 LYs, as the model assumed that those in the walking state had general population mortality).

Table E39. Breakdown of the LYs by Health State in Presymptomatic SMA Model

Undiscounted LYs	Permanent Ventilation	Not Sitting	Sitting	Walking	Total Undiscounted LYs
BSC	0.49	0.42	8.78	7.87	17.55
Spinraza	0.00	0.63	9.74	52.91	63.28

BSC: best supportive care, LY: life-year

The breakdown of discounted LYs and QALYs according to health state for the different interventions are presented below in Tables E40 and E41. These results followed the same pattern as Table E39, but the absolute numbers are lower due to discounting (for discounted LYs) and the use of QoL weights (see Table 4.5) for discounted QALYs. The utilities increased as patients achieved milestones, and the majority of the QALYs for the BSC arm were accrued by the 30% of patients in the “sitting” state, while in the Spinraza arm, a majority of the QALYs were from the patients who are in the “walking” state.

Table E40. Discounted LYs by Health State in the Presymptomatic SMA Model

Discounted LYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted LYs
BSC	0.46	0.41	5.64	3.00	9.51
Spinraza	0.00	0.63	6.35	19.61	26.58

LY: life-year

Table E41. Discounted QALYs by Health State in the Presymptomatic SMA Model

Discounted QALYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted QALYs
BSC	0.09	0.08	3.39	2.70	6.25
Spinraza	0.00	0.18	4.12	17.63	21.94

QALY: quality adjusted life-year

The breakdown of the discounted costs according to health state for the different interventions is presented below in Table E42. The costs are presented separately for treatment, administration costs and non-treatment health care.

BSC costs are solely the health care costs associated with patients being in a given health state. The majority of the costs were accrued by patients in the “sitting” state. For Spinraza, as seen in Table E38, treatment costs made up the majority of overall costs. In the Spinraza arm, the treatment costs were broadly proportional to the LYs gained in each health state, because the model assumed that patients are on Spinraza treatment for the entire life time. The discontinuation rule did not apply here, as all patients are in “sitting” or “walking” states.

In the Spinraza arm, the patients in the “sitting” and “walking” health states had higher LYs and accrue further costs, even though the costs associated with those health states (\$6,357 and \$2,499 per month, respectively) were lower than costs associated with “not sitting” and “permanent ventilation” health states (\$25,517 and \$28,218 per month).

Table E42. Discounted Costs by Health State

Treatment Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	--	\$665,506	\$2,413,760	\$7,488,868	\$10,568,134
Administration Costs	Ventilated	Not sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	--	\$6,311	\$22,889	\$71,014	\$100,214
Health Care Costs	Ventilated	Not sitting	Sitting	Walking	Total
BSC	\$155,387	\$125,487	\$430,424	\$89,843	\$801,140
Spinraza	--	\$191,725	\$484,022	\$587,986	\$1,263,733

Probabilistic Sensitivity Analyses Results for Presymptomatic SMA Model

This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis (PSA) for Spinraza versus BSC in the presymptomatic SMA Model. Due to lack of data, the distributions used for costs and utilities in the PSA are mean values $\pm 20\%$. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses. Figure E9 presents the cost-effectiveness clouds (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Spinraza versus BSC in the presymptomatic SMA Model.

Figure E9. Cost-Effectiveness Clouds for Spinraza versus BSC in Presymptomatic SMA Model

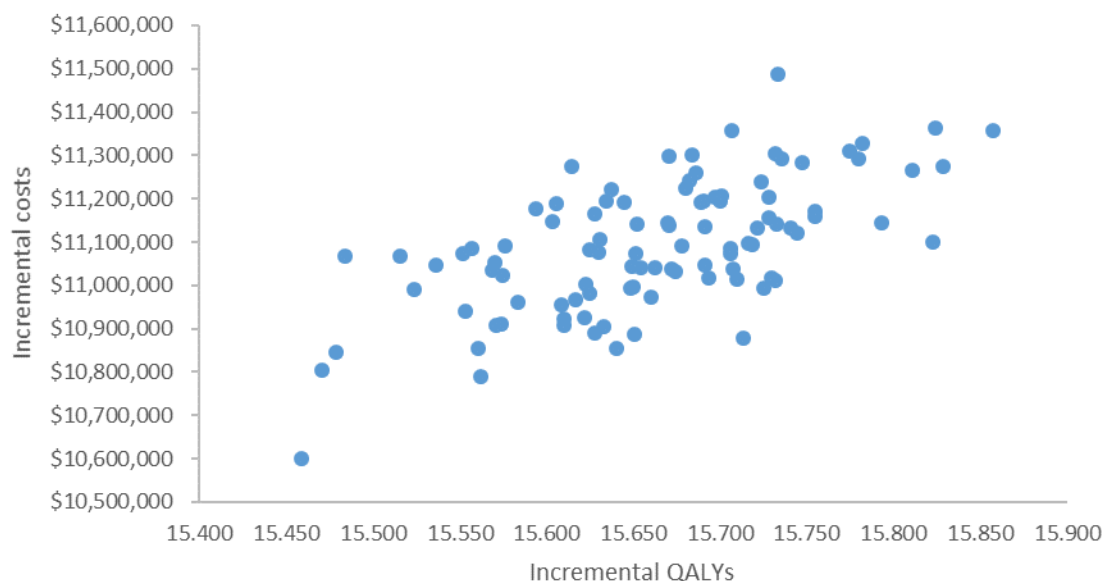
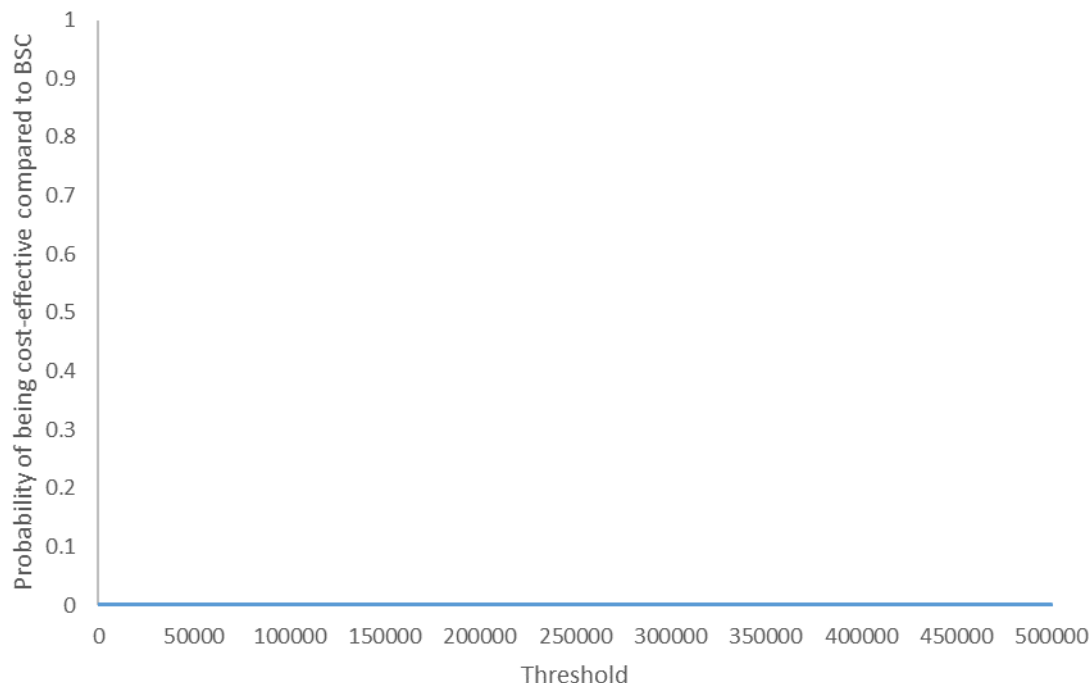


Figure E10 below presents the cost-effectiveness acceptability curve for Spinraza versus BSC in the presymptomatic SMA Model. Spinraza had zero likelihood of being cost-effective at thresholds less than \$500,000 per QALY.

Figure E10. Cost-Effectiveness Acceptability Curve for Spinraza versus BSC in Presymptomatic SMA Model



Scenario Analyses Results for Presymptomatic SMA Model

We performed a number of scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results.

In scenario analysis #1, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc.

In scenario analysis #2, we used lower health state costs of \$10,434 for the “not sitting” health state and \$13,135 for the “permanent ventilation” health state.

In scenario analysis #3, we used lower utilities of 0.5 for the “sitting” health state and 0.7 for the “walking” health state.

In scenario analysis #4, we assumed roughly half the mean survival for the “sitting” and “walking” health states. This led to a mean survival of 15.6 years and 39.65 years for the “sitting” and “walking” health states, respectively. This scenario was implemented using HRs of 5 and 16 to the survival curves for “sitting” and “walking” health states, respectively. Also, for face validity, we

imposed a constraint that the survival in “sitting” health state cannot be greater than “walking” health state.

In scenario analysis #5, we used the assumptions in scenarios #3 and #4 together (i.e., both roughly half the mean survival and lower utilities for the “sitting” and “walking” health states).

In Scenario analysis #6, we use a 10-year time horizon and in scenario analysis #7 we use 1.5% discount rate for both costs and QALYs.

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as a utility of 0.19 for the “not sitting” health state and a utility of 0.6 for the “sitting” health state in both the BSC and Spinraza arms.

Table E43 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALY gains in the Spinraza arm were lower, resulting in less favorable cost effectiveness ratios compared to base-case analyses.

Table E43. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$10,568,000	\$1,364,000	\$11,932,000	21.56	26.58	\$727,000	\$652,000
BSC	--	\$801,000	\$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation Health States – Health Care Sector Perspective

Table E44 presents the results for Spinraza versus BSC using the health care sector perspective for the scenario analysis assuming lower costs of \$10,434 for the “not sitting” health state and \$13,135 for the “permanent ventilation” health state.

Table E44. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$10,568,000	\$1,251,000	\$11,819,000	21.94	26.58	\$712,000	\$655,000
BSC	--	\$644,000	\$644,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Health Care Sector Perspective

Table E45 presents the results for the health care sector perspective for the scenario analysis assuming lower utilities of 0.5 for the “sitting” health state and 0.7 for the “walking” health state.

Table E45. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$10,568,000	\$1,364,000	\$11,932,000	17.40	26.58	\$904,000	\$652,000
BSC	--	\$801,000	\$801,000	5.08	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Health Care Sector Perspective

Table E46 presents the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival for “sitting” and “walking” health states. That resulted in a mean survival of 15.6 years and 39.65 years for the “sitting” and “walking” health states, respectively. This scenario was implemented using HRs of 5 and 16 to the survival curves for “sitting” and “walking” health states, respectively. Also, for face validity, we imposed a constraint that the survival in “sitting” health state cannot be greater than “walking” health state. As such, there high mortality in the first couple of years in the “sitting” and “walking” health states in the BSC arm as it uses the survival curves directly (due to lack of short-term data on these presymptomatic patients without treatment). However, as we use short-term data from NURTURE in the Spinraza arm, there is a survival advantage biased towards Spinraza. And as such, the ICER is lower in this analysis although the absolute QALY gains are lower.

Table E46. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$8,126,000	\$1,061,000	\$9,187,000	16.89	20.19	\$678,000	\$628,000
BSC	--	\$615,000	\$615,000	4.24	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Survival and Lower Utility for Sitting and Walking Health States – Health Care Sector Perspective

Table E47 presents the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival and lower utilities for the “sitting” and “walking” health states, respectively.

Table E47. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$8,126,000	\$1,061,000	\$9,187,000	13.21	20.19	\$877,000	\$628,000
BSC	--	\$615,000	\$615,000	3.43	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Using 10-Year Time Horizon – Health Care Sector Perspective

Tables E48 presents the results for the health care sector perspective for the scenario analysis using a 10-year time horizon.

Table E48. Using a 10-Year Time Horizon for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$3,685,000	\$605,000	\$4,290,000	6.74	8.62	\$890,000	\$870,000
BSC	--	\$500,000	\$500,000	2.48	4.27	--	--

Scenario Analysis Using 1.5% Discounting for Costs and QALYs – Health Care Sector Perspective

Tables E49 presents the results for the health care sector perspective for the scenario analysis using 1.5% discounting for both costs and QALYs.

Table E49. Using 1.5% Discounting for Spinraza versus BSC in in Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$15,203,000	\$1,837,000	\$17,040,000	32.08	38.69	\$679,000	\$612,000
BSC	--	\$953,000	\$953,000	8.38	12.39	--	--

Appendix F. Supportive Care Clinical Guidelines

Cure SMA Working Group

Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening (2018)¹¹⁰

In its 2018 treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. The group recommends the development of dependable and validated screening techniques to enable treatment of presymptomatic patients who may be more responsive to treatment than those already experiencing symptoms. For patients with SMA Types II or III with three or fewer copies of the *SMN2* gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of *SMN2* who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, but the working group recommends against immediate treatment with a disease modifying therapy.

The working group offers further recommendations for patients with four or more copies of *SMN2* who are not immediately treated with a disease modifying therapy. Overall, the group states that the clinical judgment of the physician, as well as the patient and family's wishes, should be the overarching factor in determining treatment. Ideally, the patient should meet every three to six months with a neuromuscular specialist to assess disease progress; once the patient reaches two years of age, visits can occur every six to twelve months. Follow-up assessments should include electromyography, compound muscular action potential monitoring, and myometry.

Working Group on Behalf of SMA Care Group

Diagnosis and Management of Spinal Muscular Atrophy: Part 1: Recommendations for Diagnosis, Rehabilitation, Orthopedic and Nutritional Care (2017)¹¹

The International Conference on the Standard of Care for SMA published a consensus statement in 2007; in 2017, the group issued this update to the previous statement. In the new consensus statement, the group recommends genetic testing of *SMN1* and *SMN2* as the first line of examination when SMA is suspected. Testing of *SMN2* should be conducted primarily to determine the severity of the condition. If a diagnosis is confirmed, the patient and family should be referred to a genetic counselor, and in many cases, the family should be offered psychological support.

Further, the group recommends a multidisciplinary approach to care, and advises that all specialist visits and assessments should be arranged by a neurologist familiar with the disease. A collaborative approach allows physicians and families to be proactive in patient care, which may positively influence disease trajectory. After diagnosis and every six months thereafter, the patient should undergo a physical examination to determine whether or to what degree musculoskeletal and functional impairments are present. This examination should focus primarily on motor function that may affect daily life.

The group offers separate recommendations for patients who are able to sit and for those who are not, but overall emphasizes that regular physical therapy is important to influencing the trajectory of disease. For sitters, the aim of physical therapy is to prevent contractures and scoliosis, and to maintain or restore motor function. For non-sitters, the group notes that the techniques may vary based on disease severity, but should include stretching and positioning exercises. The group recommends power wheelchairs, adapted seating systems, and assistive technology for both sitters and non-sitters. Prophylactic chest physiotherapy to promote airway clearance and ventilation is essential for both sitters and non-sitters. All patients with SMA should be assessed regularly by a nutritionist to promote growth and an appropriate diet that encourages a healthy weight and sufficient fluid, macronutrient, and micronutrient intake. Patients with SMA often experience gastrointestinal complications, and as such, should be monitored for symptoms. The group recommends swallowing studies for both sitters and non-sitters, and continued periodic nutritional evaluations.

Diagnosis and Management of Spinal Muscular Atrophy: Part 2: Pulmonary and Acute Care; Medications, Supplements and Immunizations; Other Organ Systems; and Ethics (2017)¹⁰

In the second half of the updated consensus statement, the working group offers further recommendations for patients with SMA. For both sitters and non-sitters, the group recommends clinic visits with physical examinations (every six months for sitters and every three months for non-sitters), airway clearance techniques (manual chest physiotherapy, mechanical insufflation-exsufflation, and oral suctioning devices), and positive pressure ventilation to prevent respiratory failure. Lastly, other preventive measures, such as immunizations against influenza, pneumococcus, and other respiratory viruses should be taken.



Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Draft Questions for Deliberation and Voting: March 7, 2019 Public Meeting

These questions are intended for the deliberation of the New England CEPAC voting body at the public meeting.

Clinical Evidence

Patient Population for questions 1-3: Patients with infantile-onset (Type I) spinal muscular atrophy (SMA).

1. Is the evidence adequate to demonstrate that the net health benefit of nusinersen (**Spinraza**®, Biogen Inc.) added to supportive care is superior to that provided by supportive care alone?

YesNo

2. Is the evidence adequate to demonstrate that the net health benefit of onasemnogene abeparvovec (**Zolgensma**®, AveXis/Novartis AG) added to supportive care is superior to that provided by supportive care alone?

YesNo

3. Is the evidence adequate to distinguish the net health benefit between **Spinraza** and **Zolgensma**?

YesNo

Patient Population for question 4: Patients with later-onset (Type II/III) SMA.

4. Is the evidence adequate to demonstrate the net health benefit of **Spinraza plus supportive care** is superior to that provided by **supportive care alone**?

YesNo

Patient Population for questions 5-6: Patients with presymptomatic SMA.

5. Is the evidence adequate to demonstrate the net health benefit of administering **Spinraza prior to development of symptoms** is superior to that of **supportive care alone**?

Yes

No

6. Is the evidence adequate to demonstrate the net health benefit of administering **Zolgensma prior to development of symptoms** is superior to that of **supportive care alone**?

Yes

No

Potential Other Benefits and Contextual Considerations

Spinraza

7. Is it likely that treatment with Spinraza offers one or more of the following potential “other benefits” that are not adequately captured in the base case cost-effectiveness model? (select all that apply)
- a. **Spinraza** offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.
 - b. **Spinraza** has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
 - c. **Spinraza** will significantly reduce caregiver or broader family burden.
 - d. **Spinraza** will have a significant impact on improving patients’/caregivers’ ability to return to work and/or their overall productivity.
 - e. **Spinraza** will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
 - f. There are other important benefits -- or disadvantages -- that should have an important role in judgments of the value of **Spinraza**: _____
8. Are any of the following contextual considerations important in assessing **Spinraza’s** long-term value for money? (select all that apply)
- a. **Spinraza** is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
 - b. **Spinraza** is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
 - c. **Spinraza** was the first to offer any improvement for patients with this condition.

- d. **Compared to best supportive care**, there is significant uncertainty about the long-term risk of serious side effects of **Spinraza**.
- e. **Compared to best supportive care**, there is significant uncertainty about the magnitude or durability of the long-term benefits of **Spinraza**.
- f. There are additional contextual considerations that should have an important role in judgments of the value of **Spinraza**: _____.

Zolgensma

- 9. Is it likely that treatment with **Zolgensma** offers one or more of the following potential “other benefits” that are not adequately captured in the base case cost-effectiveness model? (select all that apply)
 - a. **Zolgensma** offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.
 - b. **Zolgensma** will significantly reduce caregiver or broader family burden.
 - c. **Zolgensma** has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
 - d. **Zolgensma** will have a significant impact on improving patients’/caregivers’ ability to return to work and/or their overall productivity.
 - e. **Zolgensma** will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
 - f. There are other important benefits -- or disadvantages -- that should have an important role in judgments of the value of **Zolgensma**: _____.
- 10. Are any of the following contextual considerations important in assessing **Zolgensma**’s long-term value for money? (select all that apply)
 - a. **Zolgensma** is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
 - b. **Zolgensma** is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
 - c. **Compared to best supportive care**, there is significant uncertainty about the long-term risk of serious side effects of **Zolgensma**.
 - d. **Compared to best supportive care**, there is significant uncertainty about the magnitude or durability of the long-term benefits of **Zolgensma**.
 - e. There are additional contextual considerations that should have an important role in judgments of the value of **Zolgensma**: _____.

Long-Term Value for Money

11. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Spinraza** versus **supportive care alone** in patients with infantile-onset (Type I) SMA?

Low

Intermediate

High

12. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Zolgensma** versus **supportive care alone** in patients with infantile-onset (Type I) SMA?¹

Low

Intermediate

High

13. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Zolgensma** versus **Spinraza** in patients with infantile-onset (Type I) SMA?¹

Low

Intermediate

High

14. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Spinraza** versus **supportive care** in patients with later-onset (Type II/III) SMA?

Low

Intermediate

High

15. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treating patients with **Spinraza before symptoms develop** versus **best supportive care**?

Low

Intermediate

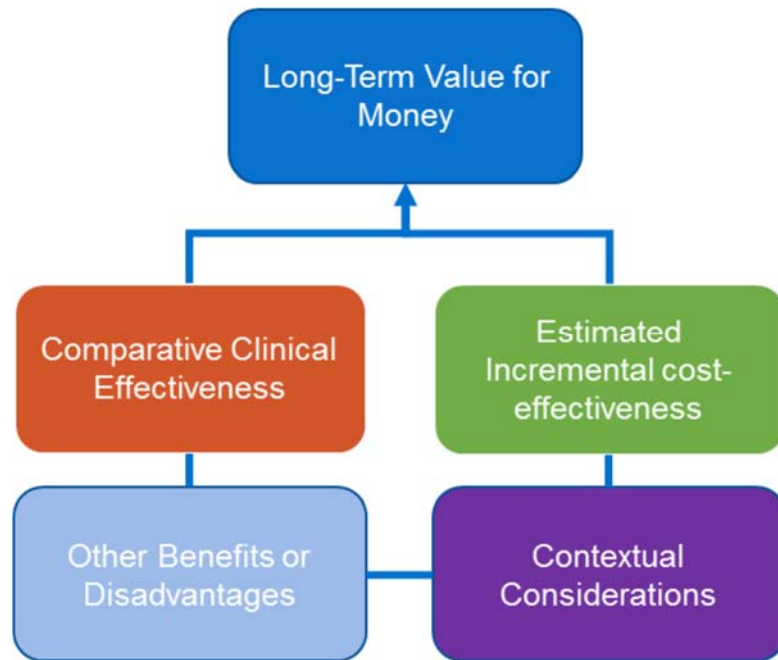
High

¹ Note: Zolgensma value votes will be taken only if the therapy's price has been announced by the time of the March 7 public meeting.

Voting Worksheets

The New England CEPAC panel votes on long-term value for money reflects careful consideration of several elements: comparative clinical effectiveness, incremental cost per outcome achieved, significant benefits/disadvantages, and contextual considerations.

Please note that ICER's value assessment framework is not a "cookbook" algorithm. Your final judgment of long-term value for money is yours to make.



Please use the following pages to write down the considerations you found most important to your final votes. ICER staff rely on these sheets to write a summary of the New England CEPAC votes for the final report.

Name: _____

Patient Population for questions 1-3: Patients with infantile-onset (Type I) spinal muscular atrophy (SMA).

1. Is the evidence adequate to demonstrate that the net health benefit of nusinersen (**Spinraza**[®], Biogen Inc.) added to supportive care is superior to that provided by supportive care alone?

Net Health Benefit

☐ Yes ☐ No

2. Is the evidence adequate to demonstrate that the net health benefit of onasemnogene abeparvovec (**Zolgensma**[®], AveXis/Novartis AG) added to supportive care is superior to that provided by supportive care alone?

Net Health Benefit

☐ Yes ☐ No

3. Is the evidence adequate to distinguish the net health benefit between **Spinraza** and **Zolgensma**?

Net Health Benefit

☐ Yes ☐ No

Patient Population for question 4: Patients with later-onset (Type II/III) SMA.

4. Is the evidence adequate to demonstrate the net health benefit of **Spinraza plus supportive care** is superior to that provided by **supportive care alone**?

Net Health Benefit

☐ Yes ☐ No

Patient Population for questions 5-6: Patients with presymptomatic SMA.

5. Is the evidence adequate to demonstrate the net health benefit of administering **Spinraza prior to development of symptoms** is superior to that of **supportive care alone** ?

Net Health Benefit

☐ Yes ☐ No

6. Is the evidence adequate to demonstrate the net health benefit of administering **Zolgensma prior to development of symptoms** is superior to that of **supportive care alone**?

Net Health Benefit

☐ Yes ☐ No

7. Is it likely that treatment with **Spinraza** offers one or more of the following potential “other benefits” that are not adequately captured in the base case cost-effectiveness model? (select all that apply)

Potential Other Benefits

- ☐ **Spinraza** offers reduced complexity compared to other treatment options that will significantly improve patient outcomes.
- ☐ **Spinraza** has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- ☐ **Spinraza** will significantly reduce caregiver or broader family burden.
- ☐ **Spinraza** will have a significant impact on improving patients’/caregivers’ ability to return to work and/or their overall productivity.
- ☐ **Spinraza** will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
- ☐ There are other important benefits or disadvantages that should have an important role in judgments of the value of **Spinraza**: _____.

8. Are any of the following contextual considerations important in assessing **Spinraza's** long-term value for money? (select all that apply)

Contextual Considerations

- ☐ **Spinraza** is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
- ☐ **Spinraza** is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
- ☐ **Spinraza** was the first to offer any improvement for patients with this condition.
- ☐ Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of **Spinraza**.
- ☐ Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of **Spinraza**.
- ☐ There are additional contextual considerations that should have an important role in judgments of the value of **Spinraza**: _____.

9. Is it likely that treatment with **Zolgensma** offers one or more of the following potential “other benefits” that are not adequately captured in the base case cost-effectiveness model? (select all that apply)

Potential Other Benefits

- ☐ **Zolgensma** offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.
- ☐ **Zolgensma** will significantly reduce caregiver or broader family burden.
- ☐ **Zolgensma** has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- ☐ **Zolgensma** will have a significant impact on improving patients’/caregivers’ ability to return to work and/or their overall productivity.
- ☐ **Zolgensma** will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
- ☐ There are other important benefits -- or disadvantages -- that should have an important role in judgments of the value of **Zolgensma**: _____.

10. Are any of the following contextual considerations important in assessing **Zolgensma's** long-term value for money? (select all that apply)

Contextual Considerations

- ☐ **Zolgensma** is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

- ☐ **Zolgensma** is intended for the care of individuals with a condition that represents a particularly high life-time burden of illness.

- ☐ Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of **Zolgensma**.

- ☐ Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of **Zolgensma**.

- ☐ There are additional contextual considerations that should have an important role in judgments of the value of **Zolgensma**: _____.

11. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Spinraza** versus **supportive care alone** in patients with infantile-onset (Type I) SMA?

Comparative Clinical Effectiveness

☐ Superior ☐ Incremental ☐ Comparable ☐ P/I ☐ Insufficient

Incremental Cost per Outcomes Achieved

☐ <\$50,000 ☐ \$50,000—\$175,000 ☐ >\$175,000

Other Benefits or Disadvantages

Contextual Considerations

Long-term Value for Money

☐ Low ☐ Intermediate ☐ High

12. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Zolgensma** versus **supportive care alone** in patients with infantile-onset (Type I) SMA?

Comparative Clinical Effectiveness

☐ Superior ☐ Incremental ☐ Comparable ☐ P/I ☐ Insufficient

Incremental Cost per Outcomes Achieved

☐ <\$50,000 ☐ \$50,000—\$175,000 ☐ >\$175,000

Other Benefits or Disadvantages

Contextual Considerations

Long-term Value for Money

☐ Low ☐ Intermediate ☐ High

13. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Zolgensma** versus **Spinraza** in patients with infantile-onset (Type I) SMA?

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☐ Superior ☐ Incremental ☐ Comparable ☐ P/I ☐ Insufficient

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☐ <\$50,000 ☐ \$50,000—\$175,000 ☐ >\$175,000

Other Benefits or Disadvantages

Contextual Considerations

Long-term Value for Money

☐ Low ☐ Intermediate ☐ High

14. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **Spinraza** versus **supportive care** in patients with later-onset (Type II/III) SMA?

Comparative Clinical Effectiveness

☐ Superior ☐ Incremental ☐ Comparable ☐ P/I ☐ Insufficient

Incremental Cost per Outcomes Achieved

☐ <\$50,000 ☐ \$50,000—\$175,000 ☐ >\$175,000

Other Benefits or Disadvantages

Contextual Considerations

Long-term Value for Money

☐ Low ☐ Intermediate ☐ High

15. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treating patients with **Spinraza before symptoms develop** versus **best supportive care**?

Comparative Clinical Effectiveness

☐ Superior ☐ Incremental ☐ Comparable ☐ P/I ☐ Insufficient

Incremental Cost per Outcomes Achieved

☐ <\$50,000 ☐ \$50,000—\$175,000 ☐ >\$175,000

Other Benefits or Disadvantages

Contextual Considerations

Long-term Value for Money

☐ Low ☐ Intermediate ☐ High

From: [Institute for Clinical and Economic Review](#)
To: [Jeffrey, Paul \(EHS\)](#)
Subject: ICER's Assessment Finds Spinraza and Zolgensma Provide Substantial Health Benefits for People with Spinal Muscular Atrophy
Date: Friday, February 22, 2019 12:29:11 PM



Institute for Clinical and Economic Review's Assessment Finds Spinraza and Zolgensma Provide Substantial Health Benefits for People with Spinal Muscular Atrophy

-- Current pricing of Spinraza would require a substantial discount to meet traditional cost-effectiveness ranges; Zolgensma's value-based price range is between \$310,000-\$900,000 using standard methodology but as high as \$1.5 million using alternative measures of health gain --

-- As with all treatments for ultra-rare conditions, judgments of overall value require consideration of contextual issues and broader benefits for patients and families; these additional factors will be discussed at a March 7 public meeting --

BOSTON, February 22, 2019 - The Institute for Clinical and Economic Review ([ICER](#)) today released an [Evidence Report](#) assessing the comparative clinical effectiveness and value of nusinersen (Spinraza®, Biogen) and onasemnogene abeparvovec (Zolgensma®, Novartis/AveXis) for the treatment of spinal muscular atrophy (SMA). Spinraza was approved in 2016 for treatment of SMA in both children and adults. Zolgensma is a gene therapy that has been studied in infants with Type I SMA, and an FDA decision is expected in the first half of 2019.

"Both of these treatments appear to dramatically improve the lives of children with SMA, as well as the families who take care of them," said David Rind, MD, ICER's Chief Medical Officer. "And while Spinraza has a broader body of evidence that provides more certainty around the health benefits patients may receive, the limited data on Zolgensma suggest that the gene therapy has the potential to deliver large benefits through a one-time treatment. Unfortunately, at its current pricing, Spinraza far surpasses common thresholds for cost-effectiveness. Among the various companies that are now bringing gene therapies to market, Novartis has a real opportunity here to demonstrate both scientific and ethical leadership by setting the launch price of Zolgensma in line with the benefits patients will likely receive."

This [Evidence Report](#) will be the subject of an upcoming [public meeting](#) of the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)), in Boston on March 7, 2019. The New England CEPAC is one of ICER's three independent evidence appraisal committees comprising medical evidence experts, practicing clinicians, methodologists, and leaders in patient engagement and advocacy.

A version of this report was previously open for a four-week [public comment](#) period. The updated [Evidence Report](#) and [voting questions](#) reflect changes made based on comments received from patient groups, clinicians, drug manufacturers, and other stakeholders. [Detailed responses to public comments can be found here.](#)

Key Clinical Findings

Evidence provides high certainty that both Spinraza and Zolgensma provide a substantial net health benefit compared to prior standard care in patients with infantile-onset (Type I) SMA. Differences in studied populations and trial design pose challenges when distinguishing between the two treatments for Type I SMA; the clinical data for Spinraza are of much higher quality—including multiple randomized, placebo-controlled trials - than those for Zolgensma.

Evidence provides moderate certainty of Spinraza's small-to-substantial benefit for patients with later-onset SMA. Spinraza also appears to be of benefit in presymptomatic SMA, with the evidence limited by the lack of published data. There are no data available to assess the net benefit of Zolgensma in presymptomatic or later-onset SMA populations.

Key Cost-Effectiveness Findings

ICER's value-based price benchmarks suggest a price range, net of any discounts and rebates, that aligns fairly with a treatment's added benefits for patients over their lifetime. The ranges reflect commonly cited cost-effectiveness thresholds of between \$100,000 and \$150,000 per Quality-Adjusted Life Year (QALY) gained.

- Based on clinical trial results and increased newborn screening in the US, in the future Spinraza appears most likely to be used to treat individuals with presymptomatic SMA. For this population, ICER's value-based price benchmark for Spinraza, inclusive of any mark-up for providers, is between \$72,000-\$130,000 for the first year of treatment when loading doses are required, and between \$36,000-\$65,000 for each successive year. Currently, excluding any mark-ups, the list price of Spinraza is \$750,000 for the initial year and \$375,000 per year thereafter.
- ICER's value-based price benchmark for Zolgensma, which is expected to be administered only once in a patient's lifetime, is between \$310,000-\$900,000 per treatment in the infantile-onset (Type I) population—the only population in which the gene therapy has been studied. Although clinicians and families will likely consider using Zolgensma also in presymptomatic infants, the data are not yet available regarding its use in this population. The FDA has yet to approve the treatment, so the labeled indication remains unknown at this time.

Consistent with ICER's [commitment to provide a broader view of cost-effectiveness](#), this Evidence Report also highlights ICER's value-based price benchmark based on a complementary measure of the ability of treatments to benefit patients: the Life Year Gained (LYG). To reach thresholds of \$100,000 and \$150,000 per LYG, Spinraza's price for presymptomatic patients would need to be between \$72,000-

\$82,000 during the initial year and \$36,000-\$41,000 per year thereafter, and Zolgensma's price for Type I patients would need to be between \$710,000-\$1.5 million per treatment.

We note that for treatments of ultra-rare disorders, insurers and other decision-makers often give added weight to contextual considerations that lead to acceptance of prices higher than those that would meet traditional cost-effectiveness ranges. Therefore, ICER's report also includes multiple threshold price analyses for both drugs, ranging from \$50,000-\$500,000 per QALY and per LYG.

[Register here to attend the New England CEPAC meeting in person or to watch by live webcast.](#)

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website](#).



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Sent by info@icer-review.org

From: [Institute for Clinical and Economic Review](#)
To: [Lenz, Kimberly \(EHS\)](#)
Subject: ICER's Assessment Finds Spinraza and Zolgensma Provide Substantial Health Benefits for People with Spinal Muscular Atrophy
Date: Friday, February 22, 2019 12:29:14 PM



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ICER's value-based price benchmarks suggest a price range, net of any discounts and rebates, that aligns fairly with a treatment's added benefits for patients over their lifetime. The ranges reflect commonly cited cost-effectiveness thresholds of between \$100,000 and \$150,000 per Quality-Adjusted Life Year (QALY) gained.

- Based on clinical trial results and increased newborn screening in the US, in the future Spinraza appears most likely to be used to treat individuals with presymptomatic SMA. For this population, ICER's value-based price benchmark for Spinraza, inclusive of any mark-up for providers, is between \$72,000-\$130,000 for the first year of treatment when loading doses are required, and between \$36,000-\$65,000 for each successive year. Currently, excluding any mark-ups, the list price of Spinraza is \$750,000 for the initial year and \$375,000 per year thereafter.
- ICER's value-based price benchmark for Zolgensma, which is expected to be administered only once in a patient's lifetime, is between \$310,000-\$900,000 per treatment in the infantile-onset (Type I) population—the only population in which the gene therapy has been studied. Although clinicians and families will likely consider using Zolgensma also in presymptomatic infants, the data are not yet available regarding its use in this population. The FDA has yet to approve the treatment, so the labeled indication remains unknown at this time.

Consistent with ICER's [commitment to provide a broader view of cost-effectiveness](#), this Evidence Report also highlights ICER's value-based price benchmark based on a complementary measure of the ability of treatments to benefit patients: the Life Year Gained (LYG). To reach thresholds of \$100,000 and \$150,000 per LYG, Spinraza's price for presymptomatic patients would need to be between \$72,000-

\$82,000 during the initial year and \$36,000-\$41,000 per year thereafter, and Zolgensma's price for Type I patients would need to be between \$710,000-\$1.5 million per treatment.

We note that for treatments of ultra-rare disorders, insurers and other decision-makers often give added weight to contextual considerations that lead to acceptance of prices higher than those that would meet traditional cost-effectiveness ranges. Therefore, ICER's report also includes multiple threshold price analyses for both drugs, ranging from \$50,000-\$500,000 per QALY and per LYG.

[Register here to attend the New England CEPAC meeting in person or to watch by live webcast.](#)

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)), and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit [ICER's website](#).



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